CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for: 074754

Trade Name : KETOROLAC TROMETHAMINE TABLETS USP

Generic Name: Ketorolac Tromethamine Tablets USP 10mg

Sponsor : Lemmon Company

Approval Date: May 16, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074754

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074754

APPROVAL LETTERS

ANDA 74-754

Lemmon Company
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

MAY 16 1997

Dear Madam:

This is in reference to your abbreviated new drug application dated September 21, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ketorolac Tromethamine Tablets USP, 10 mg.

Reference is also made to your amendments dated May 14, 1996 and March 14, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Ketorolac Tromethamine Tablets USP, 10 mg to be bioequivalent and therefore, therapeutically equivalent to the listed drug Toradol® Tablets of Syntex Laboratories. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253.

Sincerely yours,

5/16/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074754

FINAL PRINTED LABELING

NDC 0093-0314-10

KETOROLAC TROMETHAMINE Tablets, USP

10 mg

Each tablet contains:
Ketorolac Tromethamine, USP 10 mg

Caution: Federal law prohibits dispensing without prescription.

1000 TABLETS

LEMMON

Usual Dosage: One tablet every 4 to 6 hours. See package insert for full prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

L18820 PG Iss. 4/96

LEMMON COMPANY
Sellersville, PA 18960

N 0093-0314-10 0 00

NDC 0093-0314-05

KETOROLAC TROMETHAMINE Tablets, USP

10 mg

Each tablet contains:
Ketorolac Tromethamine, USP 10 mg

Caution: Federal law prohibits dispensing without prescription.

500 TABLETS

LEMMON

Usual Dosage: One tablet every 4 to 6 hours. See package insert for full prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

L18819 PG Iss. 4/96

LEMMON COMPANY
Sellersville, PA 18960

N 0093-0314-05 6 00

NDC 0093-0314-01

KETOROLAC TROMETHAMINE Tablets, USP

10 mg

Each tablet contains:
Ketorolac Tromethamine, USP 10 mg

Caution: Federal law prohibits dispensing without prescription.

100 TABLETS

LEMMON

Usual Dosage: One tablet every 4 to 6 hours. See package insert for full prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

L18818 PG Iss. 4/96

LEMMON COMPANY
Sellersville, PA 18960

00

N 0093-0314-01

KETOROLAC TROMETHAMINE
TABLETS USP, 10 mg
0314

WARNING

Ketorolac tromethamine, a nonsteroidal anti-inflammatory drug (NSAID), is indicated for the short-term (up to 5 days) management of moderately severe, acute pain, that requires analgesia at the opioid level. It is NOT indicated for minor or chronic painful conditions. Ketorolac tromethamine is a potent NSAID analgesic, and its administration carries many risks. The resulting NSAID-related adverse events can be serious in certain patients for whom ketorolac tromethamine is indicated, especially when the drug is used inappropriately. Increasing the dose of ketorolac tromethamine beyond the label recommendations will not provide better efficacy but will result in increasing the risk of developing serious adverse events.

GASTROINTESTINAL EFFECTS

- Ketorolac tromethamine can cause peptic ulcers, gastrointestinal bleeding and/or perforation. Therefore, ketorolac tromethamine is CONTRAINDICATED in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation, and in patients with a history of peptic ulcer disease or gastrointestinal bleeding.

RENAL EFFECTS

- Ketorolac tromethamine is CONTRAINDICATED in patients with advanced renal impairment and in patients at risk for renal failure due to volume depletion (see WARNINGS).

RISK OF BLEEDING

- Ketorolac tromethamine inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostasis, and those at high risk of bleeding (see WARNINGS and PRECAUTIONS).
- Ketorolac tromethamine is CONTRAINDICATED as prophylactic analgesic before any major surgery, and is CONTRAINDICATED intra-operatively when hemostasis is critical because of the increased risk of bleeding.

HYPERSENSITIVITY

- Hypersensitivity reactions, ranging from bronchospasm to anaphylactic shock, have occurred and appropriate counteractive measures must be available when administering the first dose of ketorolac tromethamine-IV/IM (see CONTRAINDICATIONS and WARNINGS). It is CONTRAINDICATED in patients with previously demonstrated hypersensitivity to ketorolac tromethamine, or allergic manifestations to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).

LABOR, DELIVERY, AND NURSING

- The use of ketorolac tromethamine in labor and delivery is CONTRAINDICATED because it may adversely affect fetal circulation and inhibit uterine contractions.
- The use of ketorolac tromethamine is CONTRAINDICATED in nursing mothers because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates.

CONCOMITANT USE WITH NSAIDs

- Ketorolac tromethamine is CONTRAINDICATED in patients currently receiving ASA or NSAIDs because of the cumulative risk of inducing serious NSAID-related side effects.

DOSAGE AND ADMINISTRATION

KETOROLAC TROMETHAMINE TABLETS

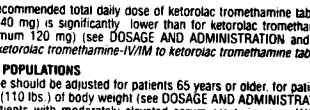
- Ketorolac tromethamine tablets are indicated only as continuation therapy to ketorolac tromethamine-IV/IM, and the combined duration of use of ketorolac tromethamine-IV/IM and ketorolac tromethamine tablets is not to exceed 5 (five) days, because of the increased risk of serious adverse events.
- The recommended total daily dose of ketorolac tromethamine tablets (maximum 40 mg) is significantly lower than for ketorolac tromethamine-IV/IM (maximum 120 mg) (see DOSAGE AND ADMINISTRATION and *Transition from ketorolac tromethamine-IV/IM to ketorolac tromethamine tablets).*

SPECIAL POPULATIONS

- Dosage should be adjusted for patients 65 years or older, for patients under 50 kg (110 lbs.) of body weight (see DOSAGE AND ADMINISTRATION), and for patients with moderately elevated serum creatinine (see WARNINGS). Doses of ketorolac tromethamine-IV/IM are not to exceed 60 mg (total dose per day) in these patients.

DESCRIPTION

Ketorolac tromethamine is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs). The chemical name for ketorolac tromethamine is (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol. The structural formula is:



$C_{19}H_{24}N_2O_6$ M.W. 376.41

Ketorolac tromethamine is a racemic mixture of (-)S and (+)R ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. Ketorolac tromethamine has a pKa of 3.5 and an n-octanol/water partition coefficient of 0.26.

Each tablet, for oral administration, contains 10 mg ketorolac tromethamine. In addition, each tablet contains the following inactive ingredients: hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID). Ketorolac tromethamine inhibits synthesis of prostaglandins and may be considered a peripherally acting analgesic. The biological activity of ketorolac tromethamine is associated with the S-form. Ketorolac tromethamine possesses no sedative or anxiolytic properties.

Pain relief was statistically different after ketorolac tromethamine dosing from that of placebo at 1/2 hour (the first time point at which it was measured) following the largest recommended doses of ketorolac tromethamine, and by 1 hour following the smallest recommended doses. The peak analgesic effect occurred within 2 to 3 hours and was not statistically significantly different over the recommended dosage range of ketorolac tromethamine. The greatest difference between large and small doses of ketorolac tromethamine by either route was in the duration of analgesia.

Pharmacokinetics

Ketorolac tromethamine is a racemic mixture of (-)S- and (+)R-enantiomeric forms, with the S-form having analgesic activity.

Comparison of IV, IM, and Oral Pharmacokinetics: The pharmacokinetics of ketorolac tromethamine following IV, IM, and oral doses of ketorolac tromethamine, are compared in Table 1. The extent of bioavailability following administration of the oral and IM forms of ketorolac tromethamine was equal to that following an IV bolus.

Linear Kinetics: Following administration of single oral, IM, or IV doses of ketorolac tromethamine, in the recommended dosage ranges, the clearance of the racemate does not change. This implies that the pharmacokinetics of ketorolac tromethamine in humans, following single or multiple IM, IV, or recommended oral doses of ketorolac tromethamine, are linear. At the higher recommended doses, there is a proportional increase in the concentrations of free and bound racemate.

Binding and Distribution: The ketorolac tromethamine racemate has been shown to be highly protein-bound (99%). Nevertheless, even plasma concentrations as high as 10 mcg/mL will only occupy approximately 5% of the albumin binding sites. Thus, the unbound fraction for each enantiomer will be constant over the therapeutic range. A decrease in serum albumin, however, will result in increased free drug concentrations.

The mean apparent volume (V_d) of ketorolac tromethamine following complete distribution was approximately 13 liters. This parameter was determined from single dose data.

Metabolism: Ketorolac tromethamine is largely metabolized in the liver. The metabolic products are hydroxylated and conjugated forms of the parent drug. The products of metabolism, and some unchanged drug, are excreted in the urine.

Clearance and Excretion: A single-dose study with 10 mg ketorolac tromethamine (racemic) demonstrated that the S-enantiomer is cleared approximately two times faster than the R-enantiomer, and that the clearance was independent of the route of administration. This means that the ratio of S/R plasma concentrations decreases with time after each dose. There is little or no inversion of the R- to S- form in humans. The clearance of the racemate in normal subjects, elderly individuals, and in hepatically and renally impaired patients, is outlined in Table 2.

The half-life of the ketorolac tromethamine S-enantiomer was approximately 2.5 hours (SD ± 0.4) compared with 5 hours (SD ± 1.7) for the R-enantiomer. In other studies, the half-life for the racemate has been reported to lie within the range of 5-6 hours.

Accumulation: Ketorolac tromethamine administered as an IV bolus, every 6 hours, for 5 days, to healthy subjects (n=13), showed no significant difference in C_{max} on Day 1 and Day 5. Trough levels averaged 0.29 mcg/mL (SD ± 0.13) on Day 1 and 0.55 mcg/mL (SD ± 0.23) on Day 6. Steady-state was approached after the fourth dose.

Accumulation of ketorolac tromethamine has not been studied in special populations (elderly patients, renal failure patients, or hepatic disease patients).

Effect of Food: Oral administration of ketorolac tromethamine tablets after a high fat meal resulted in decreased peak and delayed time-to-peak concentrations of ketorolac tromethamine by about 1 hour. Antacids did not affect the extent of absorption.

Kinetics in Special Populations -

Elderly Patients: Based on single-dose data only, the half-life of the ketorolac tromethamine racemate increased from 5 to 7 hours in the elderly (65-78 years) compared with young healthy volunteers (24-35 years) (see Table 2). There was little difference in the C_{max} for the two groups (elderly, 2.52 mcg/mL ± 0.77; young, 2.99 mcg/mL ± 1.03) (see PRECAUTIONS - Use in the Elderly).

Renally Impaired Patients: Based on single-dose data only, the mean half-life of ketorolac tromethamine in renally impaired patients is between 6 and 19 hours, and is dependent on the extent of the impairment. There is poor correlation between creatinine clearance and total ketorolac tromethamine clearance in the elderly and populations with renal impairment (r=0.5).

In patients with renal disease, the AUC∞ of each enantiomer increased by approximately 100% compared with healthy volunteers. The volume of distribution doubles for the S-enantiomer and increases by 1/5th for the R-enantiomer. The increase in volume of distribution of ketorolac tromethamine implies an increase in unbound fraction.

The AUC∞-ratio of the ketorolac tromethamine enantiomers in healthy subjects and patients remained similar, indicating there was no selective excretion of either enantiomer in patients compared to healthy subjects (see WARNINGS--Renal Effects).

Hepatic Effects: There was no significant difference in estimates of half-life, AUC∞, C_{max}, in 7 patients with liver disease compared to healthy volunteers (see PRECAUTIONS--Hepatic Effects).

TABLE 1
Table of Approximate Average Pharmacokinetic Parameters (Mean ± SD) Following Oral, Intramuscular and Intravenous Doses of Ketorolac Tromethamine

Pharmacokinetic Parameters (units)	Oral +	Intramuscular ⊙			Intravenous Bolus ϕ	
	10 mg	15 mg	30 mg	60 mg	15 mg	30 mg
Bioavailability (relative)	100%					
T_{max} (hrs)	44 ± 34	33 ± 21**	44 ± 29	33 ± 21**	1.1 ± 0.7**	2.9 ± 1.8
C_{max} (mcg/mL) (single dose)	0.87 ± 0.22	1.14 ± 0.32**	2.42 ± 0.68	4.55 ± 1.27**	2.47 ± 0.51**	4.65 ± 0.96
C_{max} (mcg/mL) (steady state q.i.d.)	1.05 ± 0.26**	1.56 ± 0.44**	3.11 ± 0.87**	N/A++	3.09 ± 1.17**	6.85 ± 2.61
C_{min} (mcg/mL) (steady state q.i.d.)	0.29 ± 0.07**	0.47 ± 0.13**	0.93 ± 0.26**	N/A	0.61 ± 0.21**	1.04 ± 0.35
C_{av} (mcg/mL) (steady state q.i.d.)	0.59 ± 0.2**	0.94 ± 0.29**	1.88 ± 0.59**	N/A	1.09 ± 0.3**	2.17 ± 0.59
V_d (L/kg)	0.175 ± 0.039				0.21 ± 0.044	

% Dose metabolized = <50
% Dose excreted in urine = 91
% Dose excreted in feces = 6
% Plasma protein binding = 99
+ Derived from PO pharmacokinetic studies in 77 normal fasted volunteers
1 Time-to-peak plasma concentration
2 Peak plasma concentration
⊙ Derived from IM pharmacokinetic studies in 54 normal volunteers
3 Trough plasma concentration
ϕ Derived from IV pharmacokinetic studies in 24 normal volunteers
4 Average plasma concentration
++Not Applicable because 60 mg is only recommended as a single-dose
5 Volume of Distribution
**Mean value was simulated from observed plasma concentration data and standard deviation was simulated from percent coefficient of variation for observed C_{max} and T_{max} data

TABLE 2
The Influence of Age, Liver and Kidney Function, on the Clearance and Terminal Half-Life of Ketorolac Tromethamine (IM[1] and Oral[2])

Types of Subjects	Total Clearance (ml/min/kg)[3]		Terminal Half-life (in hours)	
	IM Mean (range)	ORAL Mean (range)	IM Mean (range)	ORAL Mean (range)
Normal Subjects IM (n=54 mean age=32, range=18-60 Oral (n=77; mean age=32 range=20-60	0.023 (0.01 - 0.046)	0.025 (0.013 - 0.05)	5.3 (3.5 - 9.2)	5.3 (2.4 - 9)
Healthy Elderly Subjects IM (n=13), Oral (n=12) mean age=72, range=65-78	0.019 (0.013 - 0.034)	0.024 (0.018 - 0.034)	7 (4.7 - 8.6)	6.1 (4.3 - 7.6)
Patients with Hepatic Dysfunction IM and Oral (n=7) mean age=51, range=43-64	0.029 (0.013 - 0.066)	0.033 (0.019 - 0.051)	5.4 (2.2 - 6.9)	4.5 (1.6 - 7.6)
Patients with Renal Impairment IM (n=25), Oral (n=9; serum creatinine=1.9-5 mg/dL, mean age (IM)=54, range=35-71 mean age (oral)=57, range=39-70	0.015 (0.005 - 0.043)	0.016 (0.007 - 0.052)	10.3 (5.9 - 19.2)	10.8 (3.4 - 18.9)
Renal Dialysis Patients IM and Oral (n=9; mean age=40, range=27-63	0.016 (0.003 - 0.036)	———	13.6 (8 - 39.1)	———

1 Estimated from 30 mg single IM doses of ketorolac tromethamine
2 Estimated from 10 mg single oral doses of ketorolac tromethamine
3 Liters/hour/kilogram
IV Administration in normal subjects (n=37) the total clearance of 30 mg IV administered ketorolac tromethamine was 0.03 (0.017-0.051) L/kg/hr. The terminal half-life was 5.6 (4.7-9) hours.

Clinical Studies

The analgesic efficacy of intramuscularly, intravenously and orally administered ketorolac tromethamine was investigated in two postoperative pain models, general surgery (orthopedic, gynecologic and abdominal) and oral surgery (removal of impacted third molars). The studies were double-blind, single- and multiple-dose, parallel trial designs, in patients with moderate to severe pain at baseline. Ketorolac tromethamine-IV/IM was compared as follows: IM to meperidine or morphine administered intramuscularly, and IV to morphine administered either directly IV or through a PCA (Patient-Controlled Analgesia) pump.

Short-Term Use (up to 5 days) Studies: In the comparisons of intramuscular administration during the first hour, the onset of analgesic action was similar for ketorolac tromethamine and the narcotics, but the duration of analgesia was longer with ketorolac tromethamine than with the opioid comparators meperidine or morphine.

In a multi-dose, postoperative (general surgery) double-blind trial of ketorolac tromethamine-IM 30 mg versus morphine 6 and 12 mg IM, each drug given on an "as needed" basis for up to 5 days, the overall analgesic effect of ketorolac tromethamine-IM 30 mg was between that of morphine 6 and 12 mg. The majority of patients treated with either ketorolac tromethamine or morphine were dosed for up to 3 days; a small percentage of patients received 5 days of dosing.

In clinical settings where perioperative morphine was allowed, ketorolac tromethamine-IV 30 mg, given once or twice as needed, provided analgesia comparable to morphine 4 mg IV once or twice as needed.

There was relatively limited experience with 5 consecutive days of ketorolac tromethamine-IV use in controlled clinical trials, as most patients were given the drug for 3 days or less. The adverse events seen with IV-administered ketorolac tromethamine were similar to those observed with IM-administered ketorolac tromethamine, as would be expected based on the similar pharmacokinetics and bioequivalence (AUC, clearance, plasma half-life) of IV and IM routes of ketorolac tromethamine administration.

Clinical Studies with Concomitant Use of Opioids: Clinical studies in postoperative pain management have demonstrated that ketorolac tromethamine-IV/IM, when used in combination with opioids, significantly reduced opioid consumption. This combination may be useful in the subpopulation of patients especially prone to opioid-related complications. Ketorolac tromethamine and narcotics should not be administered in the same syringe.

In a postoperative study, where all patients received morphine by a PCA device, patients treated with ketorolac tromethamine-IV as fixed intermittent boluses (e.g., 30 mg initial dose followed by 15 mg q3h), required significantly less morphine (26%) than the placebo group. Analgesia was significantly superior, at various postdosing pain assessment times, in the patients receiving ketorolac tromethamine-IV plus PCA morphine as compared to patients receiving PCA-administered morphine alone.

Postmarketing Surveillance Study: A large postmarketing observational, nonrandomized study, involving approximately 10,000 patients receiving ketorolac tromethamine, demonstrated that the risk of clinically serious gastrointestinal (G.I.) bleeding was dose-dependent (see Table 3A and 3B). This was particularly true in elderly patients who received an average daily dose greater than 60 mg/day of ketorolac tromethamine (Table 3A).

JUL 6 1997

TABLE 3
Incidence of Clinically Serious G.I. Bleeding as Related to Age, Total Daily Dose, and History of G.I. Perforation, Ulcer, Bleeding (PUB) after up to 5 Days of Treatment with Ketorolac Tromethamine-IV/IM

A. Patients without History of PUB

Age of Patients	Total Daily Dose of Ketorolac Tromethamine-IV/IM			
	≤60 mg	>60 to 90 mg	>90 to 120 mg	>120 mg
<65 years of age	0.4%	0.4%	0.9%	4.6%
≥65 years of age	1.2%	2.8%	2.2%	7.7%

B. Patients with History of PUB

Age of Patients	Total Daily Dose of Ketorolac Tromethamine-IV/IM			
	≤60 mg	>60 to 90 mg	>90 to 120 mg	>120 mg
<65 years of age	2.1%	4.6%	7.8%	15.4%
≥65 years of age	4.7%	3.7%	2.8%	25%

INDICATIONS AND USAGE

Ketorolac tromethamine is indicated for the short-term (≤5 days) management of moderately severe, acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Therapy should always be initiated with ketorolac tromethamine-IV/IM, and ketorolac tromethamine tablets are to be used only as continuation treatment, if necessary. Combined use of ketorolac tromethamine-IV/IM and ketorolac tromethamine tablets is not to exceed 5 days of use because of the potential of increasing the frequency and severity of adverse reactions associated with the recommended doses (see WARNINGS, PRECAUTIONS, DOSAGE AND ADMINISTRATION, and ADVERSE REACTIONS). Patients should be switched to alternative analgesics as soon as possible, but ketorolac tromethamine therapy is not to exceed 5 days.

CONTRAINDICATIONS (see also Boxed WARNING)

- Ketorolac tromethamine is CONTRAINDICATED in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation, and in patients with a history of peptic ulcer disease or gastrointestinal bleeding.
- Ketorolac tromethamine is CONTRAINDICATED in patients with advanced renal impairment, or in patients at risk for renal failure due to volume depletion (see WARNINGS for correction of volume depletion).
- Ketorolac tromethamine is CONTRAINDICATED in labor and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine musculature, thus increasing the risk of uterine hemorrhage.
- The use of ketorolac tromethamine is CONTRAINDICATED in nursing mothers because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates.
- Ketorolac tromethamine is CONTRAINDICATED in patients with previously demonstrated hypersensitivity to ketorolac tromethamine, or allergic manifestations to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).
- Ketorolac tromethamine is CONTRAINDICATED as prophylactic analgesic before any major surgery, and is CONTRAINDICATED intra-operatively when hemostasis is critical because of the increased risk of bleeding.
- Ketorolac tromethamine inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis, and those at high risk of bleeding (see WARNINGS and PRECAUTIONS).
- Ketorolac tromethamine is CONTRAINDICATED in patients currently receiving ASA or NSAIDs because of the cumulative risks of inducing serious NSAID related adverse events.
- The concomitant use of ketorolac tromethamine and probenecid is CONTRAINDICATED.

WARNINGS (See also Boxed WARNING)
The combined use of ketorolac tromethamine-IV/IM and ketorolac tromethamine tablets is not to exceed 5 days. The most serious risks associated with ketorolac tromethamine are:

- **Gastrointestinal Ulcerations, Bleeding and Perforation:** Ketorolac tromethamine is contraindicated in patients with previously documented peptic ulcers and/or G.I. bleeding. Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated with ketorolac tromethamine. Studies to date with NSAIDs have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Postmarketing experience with parenterally administered ketorolac tromethamine suggests that there may be a greater risk of gastrointestinal ulcerations, bleeding and perforation in the elderly.

  The incidence and severity of gastrointestinal complications increases with increasing dose of, and duration of treatment with, ketorolac tromethamine. In a non-randomized, in-hospital postmarketing surveillance study, comparing parenteral ketorolac tromethamine to parenteral opioids, higher rates of clinically serious G.I. bleeding were seen in patients <65 years of age who received an average total daily dose of more than 90 mg of ketorolac tromethamine-IV/IM per day (see CLINICAL PHARMACOLOGY--Postmarketing Surveillance Study).

  The same study showed that elderly (≥65 years of age), and debilitated patients are more susceptible to gastrointestinal complications. A history of peptic ulcer disease was revealed as another risk factor that increases the possibility of developing serious gastrointestinal complications during ketorolac tromethamine therapy (see Tables 3A and B).

- **Impaired Renal Function:** ***Ketorolac tromethamine should be used with caution in patients with impaired renal function, or a history of kidney disease because it is a potent inhibitor of prostaglandin synthesis.*** Renal toxicity with ketorolac tromethamine has been seen in patients with conditions leading to a reduction in blood volume and/or renal blood flow, where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of ketorolac tromethamine may cause a dose-dependent reduction in renal prostaglandin formation and may precipitate acute renal failure. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics and the elderly. Discontinuation of ketorolac tromethamine-therapy is usually followed by recovery to the pretreatment state.

  Renal Effects: Ketorolac tromethamine and its metabolites are eliminated primarily by the kidneys, which, in patients with reduced creatinine clearance, will result in diminished clearance of the drug (see CLINICAL PHARMACOLOGY). Therefore, ketorolac tromethamine should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION) and such patients should be followed closely. With the use of ketorolac tromethamine, there have been reports of acute renal failure, nephritis, and nephrotic syndrome.

  Because patients with underlying renal insufficiency are at increased risk of developing acute renal failure, the risks and benefits should be assessed prior to giving ketorolac tromethamine to these patients. Hence, in patients with moderately elevated serum creatinine, it is recommended that the daily dose of ketorolac tromethamine-IV/IM be reduced by half, not to exceed 60 mg/day. Ketorolac tromethamine IS CONTRAINDICATED IN PATIENTS WITH SERUM CREATININE CONCENTRATIONS INDICATING ADVANCED RENAL IMPAIRMENT (see CONTRAINDICATIONS).

  Hypovolemia should be corrected before treatment with ketorolac tromethamine is initiated.

- **Fluid Retention and Edema:** Fluid retention, edema, retention of NaCl, oliguria, elevations of serum urea nitrogen and creatinine have been reported in clinical trials with ketorolac tromethamine. Therefore, ketorolac tromethamine should be used only very cautiously in patients with cardiac decompensation, hypertension, or similar conditions.

- **Hemorrhage:** Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet aggregation as well, use of ketorolac tromethamine in patients who have coagulation disorders should be undertaken very cautiously, and those patients should be carefully monitored. Patients on therapeutic doses of anticoagulants (e.g., heparin or dicumarol derivatives) have an increased risk of bleeding complications if given ketorolac tromethamine concurrently; therefore, physicians should administer such concomitant therapy only extremely cautiously. The concurrent use of ketorolac tromethamine and prophylactic low-dose heparin (2500-5000 units q12h), warfarin and dextrans have not been studied extensively, but may also be associated with an increased risk of bleeding. Until data from such studies are available, physicians should carefully weigh the benefits against the risks, and use such concomitant therapy in these patients only extremely cautiously. In patients who receive anticoagulants for any reason, there is an increased risk of intramuscular hematoma formation from administered ketorolac tromethamine-IM (see PRECAUTIONS--Drug Interactions). Patients receiving therapy that affects hemostasis should be monitored closely.

  In postmarketing experience, postoperative hematomas and other signs of wound bleeding have been reported in association with the perioperative use of ketorolac tromethamine-IV/IM. Therefore, perioperative use of ketorolac tromethamine should be avoided and postoperative use be undertaken with caution when hemostasis is critical (see WARNINGS and PRECAUTIONS).

- **Anaphylactoid Reactions:** Anaphylactoid reactions may occur in patients without a known previous exposure or hypersensitivity to aspirin, ketorolac tromethamine, or other NSAIDs, or in individuals with a history of angioedema, bronchospastic reactivity (e.g., asthma), and nasal polyps. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

PRECAUTIONS
General

- **Hepatic Effects:** *Ketorolac tromethamine should be used with caution in patients with impaired hepatic function, or a history of liver disease.* Treatment with ketorolac tromethamine may cause elevations of liver enzymes, and in patients with pre-existing liver dysfunction it may lead to the development of a more severe hepatic reaction. The administration of ketorolac tromethamine should be discontinued in patients in whom an abnormal liver test has occurred as a result of ketorolac tromethamine therapy.

- **Hematologic Effects:** Ketorolac tromethamine inhibits platelet aggregation and may prolong bleeding time; therefore, it is contraindicated as a pre-operative medication and caution should be used when hemostasis is critical. Unlike aspirin, the inhibition of platelet function by ketorolac tromethamine disappears within 24 to 48 hours after the drug is discontinued. Ketorolac tromethamine does not appear to affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT). In controlled clinical studies, where ketorolac tromethamine was administered intramuscularly or intravenously postoperatively, the incidence of clinically significant postoperative bleeding was 0.4% for ketorolac tromethamine compared to 0.2% in the control groups receiving narcotic analgesics.

Information for Patients
Ketorolac tromethamine is a potent NSAID and may cause serious side effects such as gastrointestinal bleeding or kidney failure, which may result in hospitalization and even fatal outcome.

Physicians, when prescribing ketorolac tromethamine should inform their patients of the potential risks of ketorolac tromethamine treatment (see Boxed WARNING, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections). *Advise patients not to give ketorolac tromethamine tablets to other family members and to discard any unused drug.* Remember that the total duration of ketorolac tromethamine therapy is not to exceed 5 (five) days.

Drug Interactions
Ketorolac is highly bound to human plasma protein (mean 99.2%).

The *in vitro* binding of ***warfarin*** to plasma proteins is only slightly reduced by ketorolac tromethamine (99.5% control vs 99.3%) when ketorolac plasma concentrations reach 5 to 10 mcg/mL. Ketorolac does not alter ***digoxin*** protein binding. *In vitro* studies indicate that, at therapeutic concentrations of ***salicylate*** (300 mcg/mL), the binding of ketorolac was reduced from approximately 99.2% to 97.5%, representing a potential two-fold increase in unbound ketorolac plasma levels. Therapeutic concentrations of ***digoxin, warfarin, ibuprofen, naproxen, piroxicam, acetaminophen, phenytoin,*** and ***tolbutamide*** did not alter ketorolac tromethamine protein binding.

In a study involving 12 volunteers, ketorolac tromethamine tablets were co-administered with a single-dose of 25 mg ***warfarin***, causing no significant changes in pharmacokinetics or pharmacodynamics of warfarin. In another study, ketorolac tromethamine-IV/IM was given with two doses of 5000 U of ***heparin*** to 11 healthy volunteers, resulting in a mean template bleeding time of 6.4 minutes (3.2-11.4 min) compared to a mean of 6 minutes (3.4-7.5 min) for heparin alone and 5.1 minutes (3.5-8.5 min) for placebo. Although these results do not indicate a significant interaction between ketorolac tromethamine and warfarin or heparin, the administration of ketorolac tromethamine to patients taking anticoagulants should be done extremely cautiously and patients should be closely monitored (see WARNINGS and PRECAUTIONS).

Ketorolac tromethamine-IV/IM reduced the diuretic response to ***furosemide*** in normovolemic healthy subjects by approximately 20% (mean sodium and urinary output decreased 17%).

Concomitant administration of ketorolac tromethamine tablets and ***probenecid*** resulted in decreased clearance of ketorolac and significant increases in ketorolac plasma levels (total AUC increased approximately 3-fold from 5.4 to 17.8 mcg/h/mL) and terminal half-life increased approximately 2-fold from 6.6 to 15.1 hours. Therefore, concomitant use of ketorolac tromethamine and probenecid is contraindicated.

Inhibition of renal ***lithium*** clearance, leading to an increase in plasma lithium concentration, has been reported with some prostaglandin synthesis inhibiting drugs. The effect of ketorolac tromethamine on plasma lithium has not been studied, but cases of increased lithium plasma levels during ketorolac tromethamine therapy have been reported.

Concomitant administration of ***methotrexate*** and some NSAIDs has been reported to reduce the clearance of methotrexate, enhancing the toxicity of methotrexate. The effect of ketorolac tromethamine on methotrexate clearance has not been studied.

In postmarketing experience, there have been reports of a possible interaction between ketorolac tromethamine-IV/IM and ***non-depolarizing muscle relaxants*** that resulted in apnea. The concurrent use of ketorolac tromethamine with muscle relaxants has not been formally studied.

Concomitant use of ***ACE inhibitors*** may increase the risk of renal impairment, particularly in volume depleted patients.

Sporadic cases of seizures have been reported during concomitant use of ketorolac tromethamine and ***antiepileptic drugs*** (phenytoin, carbamazepine).

Hallucinations have been reported when ketorolac tromethamine was used in patients taking ***psychoactive drugs*** (fluoxetine, thiothixene, alprazolam).

There is no evidence, in animal or human studies, that ketorolac tromethamine induces or inhibits hepatic enzymes capable of metabolizing itself or other drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility
An 18-month study in mice with oral doses of ketorolac tromethamine at 2 mg/kg/day (0.9 times the human systemic exposure at the recommended IM or IV dose of 30 mg q.i.d., based on area-under-the-plasma-concentration curve [AUC]), and a 24-month study in rats at 5 mg/kg/day (0.5 times the human AUC), showed no evidence of tumorigenicity.

Ketorolac tromethamine was not mutagenic in the Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac tromethamine did not cause chromosome breakage in the *in vivo* mouse micronucleus assay. At 1590 mcg/mL and at higher concentrations, ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells.

Impairment of fertility did not occur in male or female rats at oral doses of 9 mg/kg (0.9 times the human AUC) and 16 mg/kg (1.6 times the human AUC) of ketorolac tromethamine, respectively.

Pregnancy
Pregnancy Category C. Reproduction studies have been performed during organogenesis, using daily oral doses of ketorolac tromethamine at 3.6 mg/kg (0.37 times the human AUC) in rabbits and at 10 mg/kg (1 times the human AUC) in rats. Results of these studies did not reveal evidence of teratogenicity to the fetus. Oral doses of ketorolac tromethamine at 1.5 mg/kg (0.14 times the human AUC), administered after gestation day 17, caused dystocia and higher pup mortality in rats. There are no adequate and well-controlled studies of ketorolac tromethamine in pregnant women. Ketorolac tromethamine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery
The use of ketorolac tromethamine is contraindicated in labor and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine musculature, thus increasing the risk of uterine hemorrhage (see CONTRAINDICATIONS).

Lactation and Nursing
After a single administration of 10 mg of ketorolac tromethamine tablets to humans, the maximum milk concentration observed was 7.3 ng/mL and the maximum milk-to-plasma ratio was 0.037. After one day of dosing (q.i.d.), the maximum milk concentration was 7.9 ng/mL and the maximum milk-to-plasma ratio was 0.025. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers is CONTRAINDICATED.

Pediatric Use
Safety and efficacy in pediatric patients (less than 16 years of age) have not been established. Therefore, use of ketorolac tromethamine in pediatric patients is not recommended.

Use in the Elderly (≥65 years of age)
Because ketorolac tromethamine may be cleared more slowly by the elderly (see CLINICAL PHARMACOLOGY) who are also more sensitive to the adverse effects of NSAIDs (see WARNINGS—Renal Effects), extra caution and reduced dosages (see DOSAGE AND ADMINISTRATION) must be used when treating the elderly with ketorolac tromethamine. The incidences and severity of gastrointestinal complications increases with increasing dose of, and duration of treatment with, ketorolac tromethamine.

ADVERSE REACTIONS
Adverse reaction rates increase with higher doses of ketorolac tromethamine. Practitioners should be alert for the severe complications of treatment with ketorolac tromethamine, such as G.I. ulceration, bleeding and perforation, postoperative bleeding, acute renal failure, anaphylactic and anaphylactoid reactions, and liver failure (see Boxed WARNING, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION). These NSAID-related complications can be serious in certain patients for whom ketorolac tromethamine is indicated, especially when the drug is used inappropriately.

The adverse reactions listed below were reported in clinical trials as probably related to ketorolac tromethamine.

- INCIDENCE GREATER THAN 1%

[Percentage of incidence in parentheses for those events reported in 3% or more patients]

Body as a Whole: edema (4%)
Cardiovascular: hypertension
Dermatologic: pruritus, rash
Gastrointestinal: nausea (12%), dyspepsia (12%), gastrointestinal pain (13%), diarrhea (7%), constipation, flatulence, gastrointestinal fullness, vomiting, stomatitis
Hemic and Lymphatic: purpura
Nervous System: headache (17%), drowsiness (6%), dizziness (7%), sweating

- INCIDENCE 1% OR LESS

Body as a Whole: weight gain, fever, infections, asthenia
Cardiovascular: palpitation, pallor, syncope
Dermatologic: urticaria
Gastrointestinal: gastritis, rectal bleeding, eructation, anorexia, increased appetite
Hemic and Lymphatic: epistaxis, anemia, eosinophilia
Nervous System: tremors, abnormal dreams, hallucinations, euphoria, extrapyramidal symptoms, vertigo, paresthesia, depression, insomnia, nervousness, excessive thirst, dry mouth, abnormal thinking, inability to concentrate, hyperkinesis, stupor
Respiratory: dyspnea, pulmonary edema, rhinitis, cough
Special Senses: abnormal taste, abnormal vision, blurred vision, tinnitus, hearing loss
Urogenital: hematuria, proteinuria, oliguria, urinary retention, polyuria, increased urinary frequency

The following adverse events were reported from postmarketing experience.

Body as a Whole: hypersensitivity reactions such as anaphylaxis, anaphylactoid reaction, laryngeal edema, tongue edema (see Boxed WARNING, WARNINGS), myalgia.
Cardiovascular: hypotension and flushing.
Dermatologic: Lyell's syndrome, Stevens-Johnson syndrome, exfoliative dermatitis, maculo-papular rash, urticaria.
Gastrointestinal: peptic ulceration, GI hemorrhage, GI perforation (see Boxed WARNING, WARNINGS), melena, acute pancreatitis
Hemic and Lymphatic: postoperative wound hemorrhage, rarely requiring blood transfusion (see Boxed WARNING, WARNINGS, and PRECAUTIONS), thrombocytopenia, leukopenia.
Hepatic: hepatitis, liver failure, cholestatic jaundice.
Nervous System: convulsions, psychosis, aseptic meningitis.
Respiratory: asthma, bronchospasm.
Urogenital: acute renal failure (see Boxed WARNING, WARNINGS), flank pain with or without hematuria and/or azotemia, nephritis, hyponatremia, hyperkalemia, hemolytic uremic syndrome.

OVERDOSAGE
In controlled overdosage, daily doses of 360 mg of ketorolac tromethamine-IV/IM given for five days (3 times the highest recommended dose), caused abdominal pain and peptic ulcers which healed after discontinuation of dosing. Metabolic acidosis has been reported following intentional overdosage.

Dialysis does not significantly clear ketorolac tromethamine from the blood stream.

DOSAGE AND ADMINISTRATION
THE COMBINED DURATION OF USE OF KETOROLAC TROMETHAMINE-IV/IM AND KETOROLAC TROMETHAMINE TABLETS IS NOT TO EXCEED FIVE (5) DAYS. THE USE OF KETOROLAC TROMETHAMINE TABLETS IS ONLY INDICATED AS CONTINUATION THERAPY TO KETOROLAC TROMETHAMINE-IV/IM.

Ketorolac Tromethamine-IV/IM may be used as a single, or multiple dose, on a regular or "prn" schedule for the management of moderately severe, acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Hypovolemia should be corrected prior to the administration of ketorolac tromethamine (see WARNINGS--Renal Effects). Patients should be switched to alternative analgesics as soon as possible, but ketorolac tromethamine therapy is not to exceed 5 days.

Ketorolac tromethamine tablets are indicated ONLY as continuation therapy to ketorolac tromethamine-IV/IM for the management of moderately severe, acute pain that requires analgesia at the opioid level. See also PRECAUTIONS--Information for Patients.

Transition from Ketorolac Tromethamine-IV/IM to Ketorolac Tromethamine Tablets

The recommended ketorolac tromethamine tablets dose is as follows:

- Patients <65 years of age:
  Two (2) tablets as a first oral dose for patients who received **60 mg IM single dose, 30 mg IV single dose or 30 mg multiple dose** ketorolac tromethamine-IV/IM followed by one (1) tablet every 4 to 6 hours, not to exceed 40 mg/24 h of ketorolac tromethamine tablets.

- Patients ≥ 65 years of age, renally impaired and/or less than 50 kg (110 lbs.) of body weight:
  One (1) tablet as a first oral dose for patients who received **30 mg IM single dose, 15 mg IV single dose or 15 mg multiple dose** ketorolac tromethamine-IV/IM followed by one (1) tablet every 4 to 6 hours, not to exceed 40 mg/24 h of ketorolac tromethamine tablets.

Shortening the recommended dosing intervals may result in increased frequency and severity of adverse reactions.

The maximum combined duration of use (parenteral and oral ketorolac tromethamine) is limited to 5 days.

HOW SUPPLIED
Ketorolac Tromethamine Tablets USP, 10 mg are round, white, unscored, film-coated tablets debossed "93" on one side and "314" on the other side, available in bottles of 100, 500, and 1000.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense contents in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by:
LEMMON COMPANY
Sellersville, PA 18960

Printed in USA
Rev. A 4/96
118221

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074754

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO 3

2. ANDA 74-754

3. NAME AND ADDRESS OF APPLICANT
Lemmon Company
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

4. LEGAL BASIS FOR SUBMISSION
Toradol® (Syntex) NDAs 19645 (10 mg tablets) & 19698 (injection). Patent expires 05/16/97

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME Ketorolac Tromethamine Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES: see next page

10. PHARMACOLOGICAL CATEGORY
Nonsteroidal anti-inflammatory

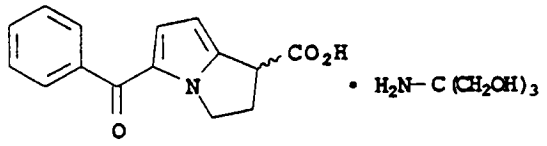
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablets

14. POTENCY
10 mg

15. CHEMICAL NAME AND STRUCTURE
(±)-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)



$C_{15}H_{13}NO_3 . C_4H_{11}NO_3$

M.W. = 376.41 CAS [*74103-07-4*]

16. RECORDS AND REPORTS N/A

17. COMMENTS Tentative approval to full approval; firm reports no changes in the application since the tentative approval. Therefore this review document merely summarizes previous reviews.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend: APPROVAL.

19. REVIEWER: J. L. Smith DATE COMPLETED: 04/08/97
Endorsements: HFD-623/J.Smith/ 4/10/97 4/10/97.
HFD-623/V.Sayeed/4-9-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074754

BIOEQUIVALENCE REVIEW(S)

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ANDA 74-754

Lemmon Company
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville PA 18960

SEP 30 1996

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Ketorolac Tromethamine Tablets USP 10 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing should be conducted as specified in the USP 23 and should be incorporated into your stability and quality control programs.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

//~~Keith~~ K. Chan, ~~Ph.D.~~
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MAR 6 1996

Ketorolac Tromethamine
10 mg tablet
Reviewer: Nhan L. Tran
ANDA 74-754

Lemmon Pharmaceuticals
Sellersville, PA
Submission date:
September 21, 1995.

Review Of Two Bioequivalence Studies (Fasting and Fed) and A Dissolution Data.

I. Background

General Note **NOT FOR FOI.**

Ketorolac tromethamine is a chiral (R and S forms) non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, antipyretic and analgesic activities. Only the S form is reported to have analgesic activity. Ketorolac tromethamine is more than 99% protein bound, mostly bound to albumin.
When given orally, the bioavailability is at least 80% and the drug does not undergo first pass metabolism. Mean plasma Cmax is about 0.87 mcg/ml after single dose of 10 mg, with a Tmax of about 40 minutes. Plasma terminal half-life is about 5 to 6 hours for the racemate. Ketorolac is mostly metabolized in the liver, and the metabolic products are largely hydroxylated and conjugated forms of the parent drug.

Oral administration of ketorolac after a high fat meal results in lowering Cmax and prolonging Tmax by about 1 hour. The extent of absorption measured by AUC, and the half-life (T1/2) are not affected.
The drug is presently marketed by Syntex under the trade name TORADOL^{R}, 10 mg tablets, and also is available in injectable dosage forms (15 mg, 30 mg and 60 mg for IM injection and 15 mg and 30 for IV Bolus injection).

II. Product Information

The lots of test and reference products used in the comparative studies are:

Test: LEMMON's ketorolac tromethamine tablets USP, 10 mg, lot # 0293-117, lot (batch) size: No expiry date, nor information on theoretical and actual yield were provided. Content uniformity: 99.2%.

Reference: SYNTEX's TORADOL^{R} (ketorolac tromethamine) 10 mg tablets, lot # 02541, expiry date: 2/96. Content uniformity: 98.7%.

SUMMARY OF THE RESULTS OF THE IN-VIVO BIOEQUIVALENCE STUDIES AND DISSOLUTION TESTING DATA

I. Product Information

The lots of test and reference products used in the comparative studies are:

Test: LEMMON's ketorolac tromethamine tablets USP, 10 mg, lot # 0293-117, lot (batch) size: Content uniformity: 99.2%.

Reference: SYNTEX's TORADOL[R] (ketorolac tromethamine) 10 mg tablets, lot # 02541, expiry date: 2/96. Content uniformity: 98.7%.

II. Review of the fasting study: Protocol # B-01085.

Objective: To compare the bioavailability of a generic ketorolac tromethamine 10 mg tablets (Lemmon Company) with that of TORADOL[R] 10 mg tablets by Syntex, in healthy male volunteers under fasting conditions.

Principal Investigator:

Clinical Study Site:

Analytical Site:

Dose: Two (2) tablets with 240 ml of water.
Number of subjects: Twenty six males (26), with NO ALTERNATES
Subject selection:
Inclusion Criteria: All males, 18 - 45 years of age, no more than ± 15% from ideal BW, with no history of cardiac, GI diseases and no alcohol or drug abuse as shown by a medical and physical exams were included in the study. Subjects should have no prescription drugs within 14 days, no alcohol consumption for at least 24 hours prior to drug administration, and no known allergy to ketorolac.

Exclusion criteria: Alcoholics, subjects with GI, renal, hepatic diseases, abnormal laboratory measurements, etc. No OTC medications nor alcohol, xanthine containing beverages were allowed during the study.
Approved IRB as well as informed consent were obtained from each subject prior to entry into the study.

Subjects were housed in the facility from at least 12 hours prior to and at least 24 hours after the drug administration. Subjects were not permitted to smoke from one hour prior to and until 4 hours after the drug administration. Washout period was at least one (1) week between dose. Subjects were fasted for at least 10 hours prior to and 5 hours after the drug administration. Water was given ad lib except within 1 hour of drug administration.

Sampling schedule: 10 ml blood sample was collected at pre-dose, and at 0.17, 0.25, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 2, 4, 6, 8, 10, 12, 15, 24, and 36 hours. Plasma was separated and frozen at -20°C until assay.

Assay Methodology:

Pharmacokinetic and statistical analyses: AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were calculated. ANOVA and 90% C.I. limits (two-one sided test) were used for all important pharmacokinetic parameters.

RESULTS

1 Analytical Methodology

2. Pharmacokinetics

According to the Sponsor, all 26 subjects completed the study. Minor adverse reactions such as emesis, diarrhea and light headache occurred in only three subjects (subj # 3, 10 and 24) and all were on reference formulation. No therapy was required. The Sponsor also indicated that no significant deviation from the study protocol, except some late blood draw. Mean plasma concentration-time profiles of all 26 subjects under test and reference treatments are shown below:

Mean Plasma concentration, ng/ml

Time (hr)	Test (%CV, N=26)	Ref (%CV, N=26)
0.	0.0	0.0
0.17	89.2 (143.6%)	118.1 (147.5%)
0.25	253.1 (108.2%)	396.1 (122.2%)
0.33	622.8 (83.4%)	878.4 (77.3%)
0.50	1402.6 (48.3%)	1489.1 (43.1%)
0.67	1460.2 (41.7%)	1441.3 (27.5%)
0.83	1383.3 (37.3%)	1368.6 (24.7%)
1.	1262.0 (37.1%)	1314.8 (24.4%)
1.25	1171.9 (28.3%)	1202.9 (24.8%)
1.5	1099.7 (26.2%)	1091.9 (22.1%)
2	969.1 (15.9%)	947.9 (22.5%)
4	565.0 (26.1%)	596.4 (31.5%)
6	343.2 (28.1%)	334.9 (30.4%)
8	226.3 (37.3%)	225.0 (30.4%)
10	177.6 (33.5%)	179.9 (48.7%)
12	126.7 (37.3%)	131.8 (47.3%)
15	73.9 (39.1%)	83.3 (45.5%)
24	24.8 (77.0%)	29.5 (60.1%)
36	0.0	0.0

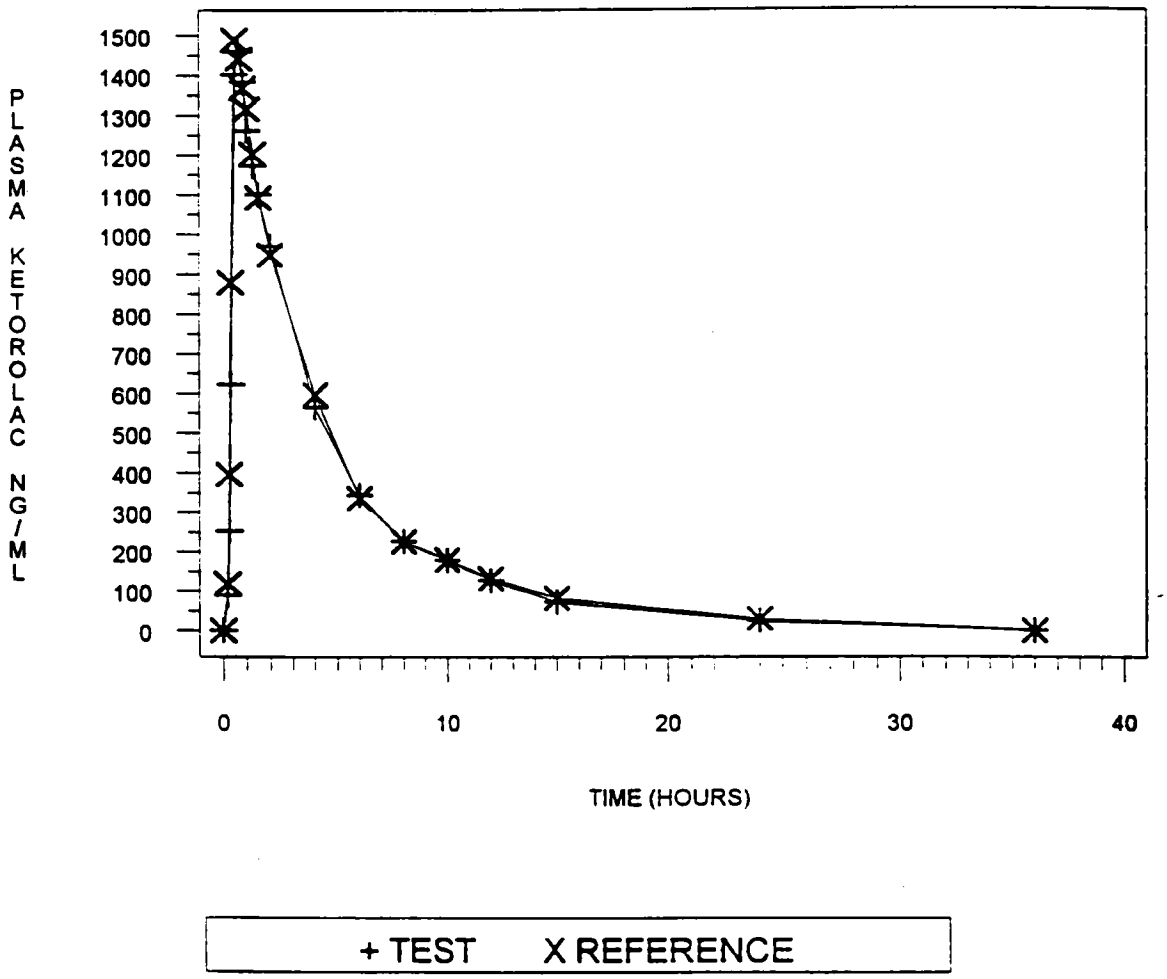
Mean values of important pharmacokinetic parameters are shown below:

Parameter	Test (%CV)	Ref (%CV)
AUC_{0-t}	6423.6 (21.1%)	6655.0 (22.1%)
$AUC_{0-\infty}$	6722.4 (20.9%)	6943.5 (22.2%)
C_{max}	1733.0 (26.6%)	1713.0 (26.7%)
T_{max} (hrs)	0.98 (80.3%)	0.904 (84.9%)
$T_{1/2}$ (hrs)	5.168 (23.3%)	5.67 (17.6%).

ANOVA was performed on all parameters and terms such as sequence, sub(sequence), period and treatment were included in the statistical model. 90% confident interval limits were estimated using two one-sided test procedure. Results indicated that, for log transformed and untransformed parameters, all parameters are within the current acceptable limits: AUCt (92.3% - 102%), AUCinf (92.9% - 102%) and Cmax (90.6% - 112%).

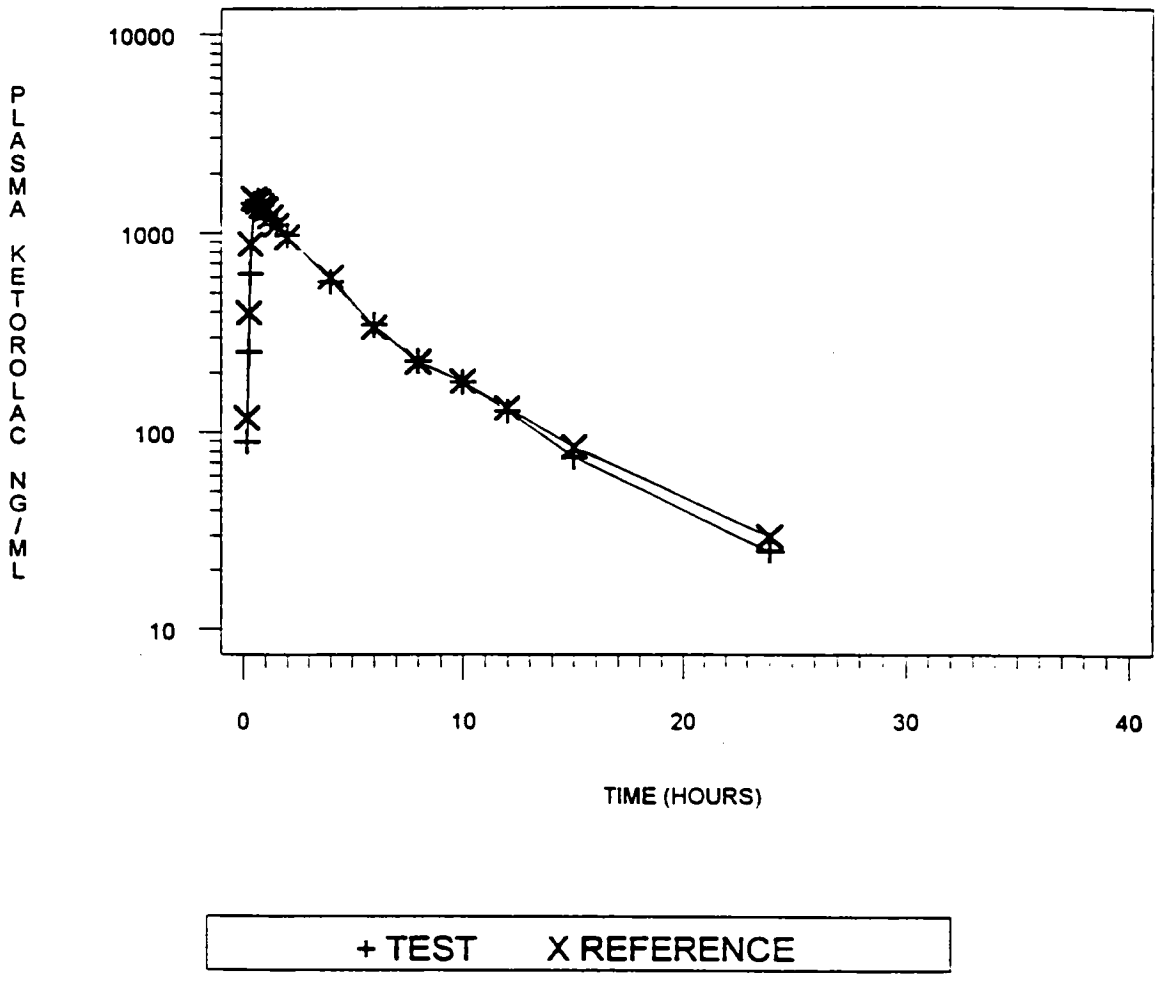
LINEAR PLOT OF

KETOROLAC MEAN DATA



SEMI-LOG PLOT OF

KETOROLAC MEAN DATA



IV. Review of the non-fasting study: Protocol # B-01095.

Objective: To compare the bioavailability of a generic ketorolac tromethamine 10 mg tablets (Lemmon Company) with that of TORADOL® 10 mg tablets by Syntex, in healthy male volunteers under fasting and fed conditions.
This will be a single dose, randomized, 3-way cross-over (test: fed and fasting, and reference: fed) in 18 subjects.

Principal Investigator: Principal Investigator

Clinical Study Site:

Analytical Site:

Dose: Two (2) tablets with 240 ml of water. The lots of test and reference products used in the comparative studies are identical to the ones used in the fasting study as follows:

Test: LEMMON's ketorolac tromethamine tablets USP, 10 mg, lot # 0293-117, lot (batch) size: No expiry date, nor information on theoretical and actual yield were provided. Content uniformity: 99.2%.

Reference: SYNTEX's TORADOL® (ketorolac tromethamine) 10 mg tablets, lot # 02541, expiry date: 2/96. Content uniformity: 98.7%.

Number of subjects: Eighteen males (18), with NO ALTERNATES The same subject selection criteria was used for the fasting and non-fasting studies.

Washout was one week between treatments.

Meal and food restriction:

Fed phase: Subjects will fast for at least 10 hours prior to serving the standard breakfast. Subjects will be instructed to eat the entire breakfast in 30 minutes and the drug will be given 35 minutes after the subjects begin the breakfast. Breakfast composition is as follows: 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hash brown potatoes, 180 ml of orange juice and 240 ml of whole milk.

Fasting phase: Subjects will fast for at least 10 hours prior to and 5 hours after drug administration.

Other procedures such as analytical, sampling schedule, are identical to the fasting study (Protocol # B-01085).

RESULTS

1 Analytical Methodology

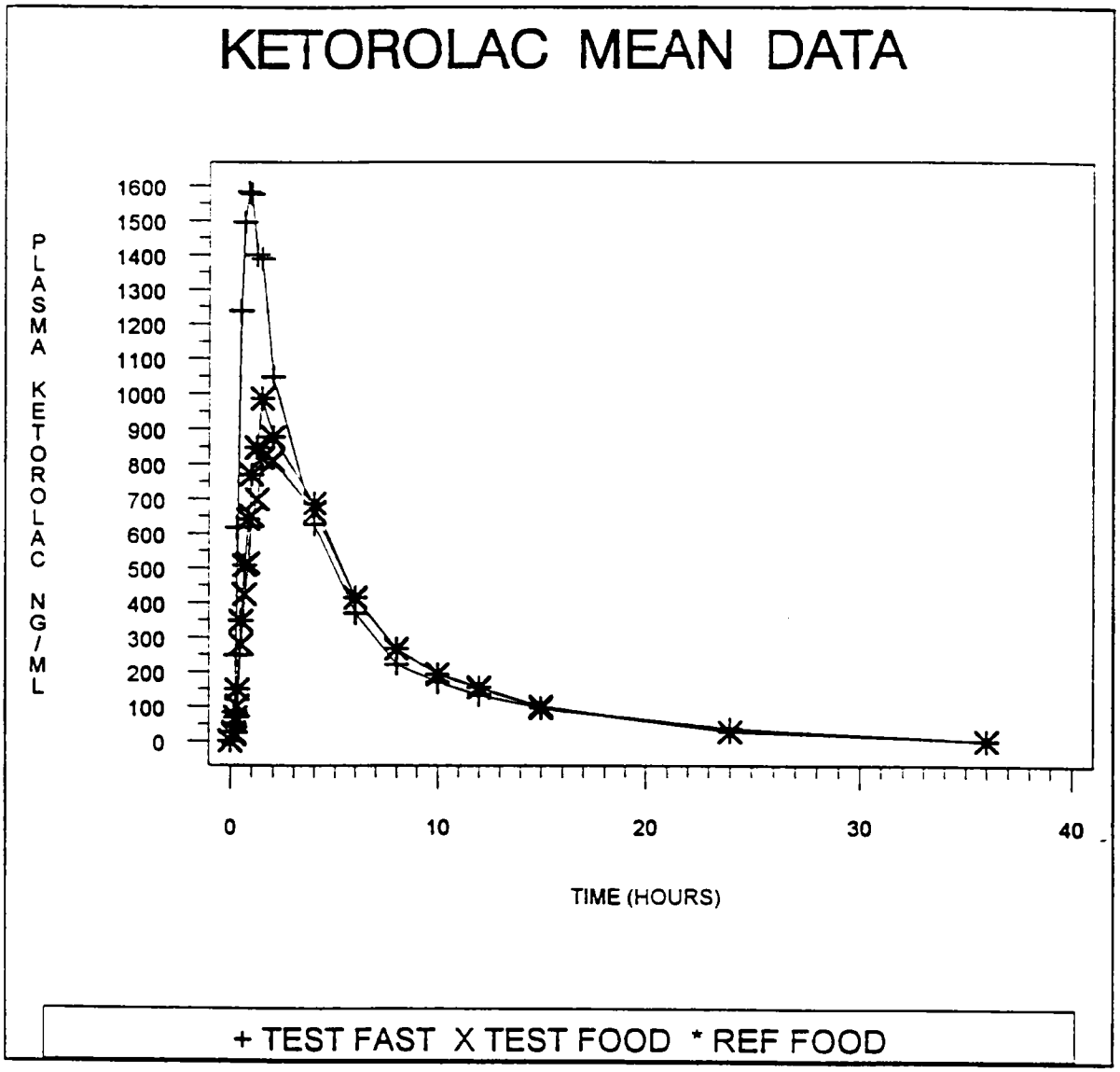
Since identical assay methodology was used for both fasting and non-fasting studies, no further assay validation data was submitted. No further information is needed on assay validation for this non-fasting study.

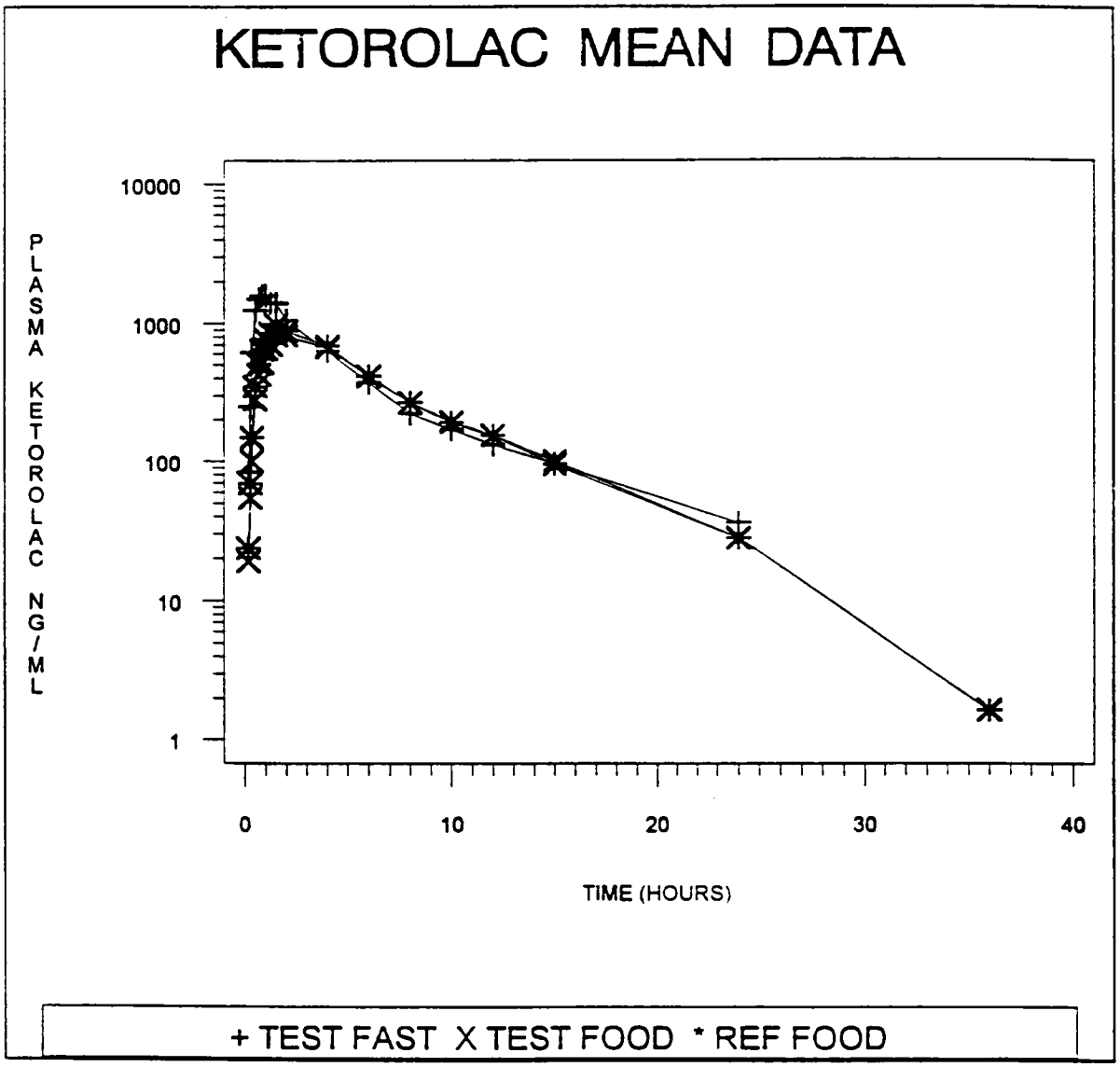
2. Pharmacokinetics

According to the Sponsor, of 18 subjects enrolled in the non-fasting study, 15 subjects completed the study. The firm reported the following drop-outs: subject #5 dropped prior to period 3 due to family situation, and 15 dropped prior to period 2 for personal reasons. The total number of subjects completing the study was 16. After the assay, the firm noticed that no valid data can be obtained from subject #9 due to problem with interferences in the chromatograms. Thus total number of subjects whose data were used for bioequivalence determination was 15. The Sponsor indicated that no adverse reactions nor protocol violations were observed in this non-fasting study, except some early or late blood draw times.

Mean plasma concentration-time profiles of all 15 subjects under fasting (test) and non-fasting (test and reference) conditions are shown below:

	Mean Plasma concentration, ng/ml		
Time (Hrs)	Test (%CV, N = 15) (Fasting)	Test (%CV, N = 15) (Fed)	Ref (%CV, N = 15) (Fed)
0.	0.0	0.0	0.0
0.17	83.85 (76.51%)	19.01 (124.55%)	23.6 (82.24%)
0.25	248.25 (55.41%)	54.48 (85.45%)	68.93 (74.92%)
0.33	615.67 (79.90%)	100.59 (81.29%)	148.59 (97.93%)
0.50	1236.93 (51.83%)	279.93 (86.72%)	347.37 (81.54%)
0.67	1493.4 (27.91%)	423.86 (79.71%)	506.7 (71.61%)
0.83	1581.67 (31.04%)	512.84 (66.83%)	640.01 (72.96%)
1.	1575.87 (23.26%)	649.55 (62.29%)	768.60 (60.42%)
1.25	1399.47 (22.61%)	697.33 (50.98%)	845.80 (50.47%)
1.5	1388.0 (26.70%)	816.73 (55.45%)	985.13 (37.10%)
2	1046.6 (20.49%)	809.4 (33.32%)	876.07 (29.47%)
4	624.0 (25.38%)	661.73 (31.07%)	685.93 (29.40%)
6	369.0 (29.43%)	412.2 (36.18%)	413.53 (39.95%)
8	221.0 (24.49%)	265.09 (41.2%)	265.87 (39.65%)
10	169.66 (27.44%)	193.26 (43.54%)	191.31 (41.03%)
12	132.13 (27.62%)	153.62 (51.97%)	154.29 (45.00%)
15	95.43 (46.51%)	100.69 (53.30%)	94.56 (41.17%)
24	36.01 (61.39%)	27.93 (80.22%)	27.79 (72.28%)
36	0.0	1.65 (387.30%)	1.627 (387.30%)


KETOROLAC MEAN DATA
PLASMA KETOROLAC NG/ML
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30
40
TIME (HOURS)
+ TEST FAST X TEST FOOD * REF FOOD


KETOROLAC MEAN DATA
PLASMA KETOROLAC NG/ML
10000
1000
100
10
1
0
10
20
30
40
TIME (HOURS)
+ TEST FAST X TEST FOOD * REF FOOD

Means (N = 15) of important pharmacokinetic parameters are shown below:

Parameter	Test (%CV) (Fast)	Test (%CV) (Fed)	Ref (%CV) (Fed)
AUC_{0-t}	7136.83 (21.88%)	5992.38 (26.05%)	6266.08 (24.37%)
$AUC_{0-\infty}$	7528.05 (22.16%)	6302.95 (25.28%)	6569.65 (23.01%)
C_{max}	1936.60 (21.58%)	1055.20 (24.40%)	1198.47 (25.07%)
$T_{max(h)}$	0.939 (32.6%)	2.0 (56.7%)	1.94 (58.8%)
$T_{1/2}(h)$	6.16 (19.8%)	5.25 (18.6%)	5.21 (14.19%)

ANOVA was performed on all parameters and terms such as sequence, sub(sequence), period and treatment were included in the statistical model. From the ANOVA output, least squares means (log transformed data) of the test and reference formulations were obtained and they were used for the estimation of the ratios of test/reference for AUCt, AUCinf, and Cmax. For the log transformed data, this ratio can be estimated as [$100xe^{(LSM_{test}-LSM_{reference})}$], with the least-squares mean (LSM) computed by using the LSMEANS statement in the SAS GLM procedure.

Results indicated that, for log transformed parameters, the ratios of the test and reference formulations under nonfasting conditions for ***AUCt (96.0%), AUCinf (96.2%) and Cmax (90.5%), all are within the current acceptable ratio limits of 80% to 125%.***

V. Composition of the test tablets

Core Tablet:

Ingredient	Amount per tablet
Ketorolac Tromethamine, USP	10 mg
Lactose Monohydrate, NF	-
Microcrystalline Cellulose, NF	
Magnesium Stearate, NF	
Total	**200 mg**

Coating:

White

VI. In Vitro Dissolution Testing

The conditions and specifications used by the firm are identical to the ones by the USP as described below:

In Vitro Dissolution Testing

Drug: Ketorolac Tromethamine, Dose Strength: 10 mg, Tablet
ANDA No.: 74-754, Firm: Lemmon
Submission Date: May 14, 1996
File Name: 74754SD.596

I. Conditions for Dissolution Testing:

USP XXII, Paddle: RPM: 50, 600 ml, water, No. Units Tested: 12
Specifications: NLT in 45 minutes
Reference Drug: TORADOL[R] 10 mg Tablets by SYNTEX.
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (min)	Test Product Lot # 293-117, Strength: 10 mg			Reference Product Lot # 2541, Strength: 10 mg.		
	Mean %	Range	%CV	Mean %	Range	%CV
15	89.6		13.5	93.5		8.2
30	97.3		7.4	98.1		4.9
45	99.0		5.5	100.3		3.6
60	99.7		4.4	101.3		3.0

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

DRUG NAME: Ketorolac ANDA #: 74-754
SPONSOR: Lemmon
DOSAGE FORM: Tablet STRENGTH: 10 mg
TYPE OF STUDY: Single dose, fasting and single dose non-fasting.
STUDY SITE:
CLINICAL:
ANALYTICAL:

NOT A FIRST GENERIC

STUDY SUMMARY

Fasting Study: This was a 2-way cross-over, fasting, in 26 subjects with no alternates. All subjects completed the study. Minor adverse reactions such as emesis, diarrhea and light headache occurred in 3 subjects, all on the reference formulation (#3, 10, and 24). No therapy was required.
90% C.I. limits on $LAUC_t$ (92.3% - 102%), $LAUC_{inf}$ (92.9% - 102%) and LC_{max} (90.6% - 112%) are within acceptable ranges.

Non Fasting Study: This was a three way, single dose food effect study in 18 subjects with no alternates. Of 18 subjects enrolled in the study, subj #5 withdrew prior to Period 3 due to family situation, #15 failed to show up for phase II dosing for personal reasons. Total number of subjects completing the study was 16. After the assay, the firm noticed that, for subject #9, there were problems with interference in the Thus no valid data can be obtained from this subject. For this nonfasting study, the number of subjects used in the statistical analysis was 15. The ratios of LSQ means for $LAUC_t$ (96%), $LAUC_{inf}$ (96.2%) and LC_{max} (90.5%) are within the acceptable limits.

Dissolution: The test tablet meets the dissolution specifications as follows:
USP XXIII, Paddle, 50 RPM
Medium: Water at 37°C, 600 ml.
Specification: NLT % in 45 minutes

PRIMARY REVIEWER: Nhan L. Tran, Ph.D. BRANCH: II
INITIAL: _____ DATE: 9-17-96

TEAM LEADER: Shrinivas Nerurkar, Ph.D. BRANCH: II
INITIAL: _____ DATE: 9-27-1996

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Keith K. Chan, Ph.D.
INITIAL: _____ DATE: 9/27/96

DIRECTOR, OFFICE OF GENERIC DRUGS:
INITIAL: _____ DATE: _____

DBE STUDY APPROVAL FORM

ANDA #:	74-754	FIRM:	Lemmon	FIRST GENERIC:	NO
DRUG:	Ketorolac	DOSAGE FORM:	Tablet	STRENGTH:	10mg
RLD:	Toradol®	FIRM:	Syntex	BIO REVIEWER:	N. Tran

Therapeutic Category: NSAID Dosage Regimen: Varied
Solubility/Permeability: High solubility/high permeability (Dissolution: NLT 75% in 45 minutes and Tmax is less than 1 hour.

FASTING STUDY:
Clinical Procedure:

Center:	Gateway Med. Res	Principal Inv.:	I. Plisco, MD
# of Subjects Planned:	26	# of Subjects Required:	26
# dropped out:	0	# of subject completed:	26
# in data analysis:	26	Subset analysis:	No
Randomization:	Yes	Demographic:	All males, age
Dose administration:	2x10mg	between 18-45, wt: not more than ±15%	
Blood sample:	No deviation was noted	from ideal body weight.	

Safety summary: Minor adverse events such as emesis, diarrhea and light headache were reported during the study for 3 subjects who were on reference formulation: Subj #3, 10, and 24. The symptom was mild and no treatment was required.

NON FASTING STUDY:
Clinical Procedure:

Center:	Gateway Med. Re	Principal Inv.:	I. Plisco, MD
# of Subjects Planned:	18	# of Subjects Required:	18
# dropped out:	2	Reasons:	Failed to return
# of subject completed:	16	# in data analysis:	15 (Samples from
Subset analysis:	N/A	subject #9 were contaminated.	
Randomization:	Yes	Demographic:	Same as in fasted study.
Dose administration:	2x10mg	Blood sample:	No deviation noted

Safety summary: For this study, there was no adverse event reported by any subject.

ANALYTICAL PROCEDURE:

Center:	Bioassay, Houston, TX	Principal Inv.:	P. Likhari
Analytical Method	HPLC		
Pre-study validation:	Accuracy:between 97.2%-102% for all QC samples. Precision: between 0.2%-2.5%, Sensitivity: 20 ng/ml		
Stability validation:	Stable for 87 days		
Within study validation:	Accuracy & precision comparable to pre-study data		
Standard curve:	20ng/ml-300ng/ml	QC Samples:	50, 350, and 2500ng/ml
Comments:	Acceptable		

PK/STATISTICAL ANALYSIS:

PK Calculation Procedure:	Trapezoidal rule for AUCs, Cmax from raw data.
Spot checked data:	No discrepancies noted
Mean Plasma Profile:	OK
Individual Plasma Profile:	Inspected and found acceptable.

SUMMARY OF PK PARAMETERS:

FASTING STUDY:

	Test	Reference	90% C.I	intra CV	inter CV	Total CV
AUC_{0-t}	6424 ng.ml/hr	6655 ng.ml/hr	92.3%-102%	9.5%	22%	31.5%
$AUC_{0-\infty}$	6722	6943	93%-102%	9.02%	22%	31%
C_{max}	1733 ng/ml	1713 ng/ml	91%-112%	20.1%	27%	47.1%

Statistical Procedure: Appropriate for 2-way cross-over.
Comments: All parameters were within the acceptable 90% C.I limits .

NON FASTING STUDY:

	Test	Reference	Ratio T/F(geo)	intra CV	inter CV	Total CV
AUC_{0-t}	5992 ng.ml/hr	6266 ng.ml/hr	96.1%	11.8%	26%	37.8%
$AUC_{0-\infty}$	6303	6597	96.2%	11.75%	25%	36.75%
C_{max}	1055 ng/ml	1198 ng/ml	90.5%	23%	25%	48%

Statistical Procedure: Appropriate for 3-way cross-over.
Comments: All parameters were within the acceptable ratio limits .

In-Vitro Dissolution:

USP XXIII Method II (Paddle), 600 ml water, 50 RPM
Specifications: NLT 75% in 45 mi.

Waiver Request: None.

Comparison to Past Generic Products: Parameters are comparable

III. Review of the fasting study: Protocol # B-01085.

Objective: To compare the bioavailability of a generic ketorolac tromethamine 10 mg tablets (Lemmon Company) with that of TORADOL^{R} 10 mg tablets by Syntex, in healthy male volunteers under fasting conditions.

Principal Investigator: , Principal Investigator

Clinical Study Site:

Analytical Site:

Dose: Two (2) tablets with 240 ml of water.

Number of subjects: Twenty six males (26), with NO ALTERNATES

Subject selection:

Inclusion Criteria: All males, 18 - 45 years of age, no more than ± 15% from ideal BW, with no history of cardiac, GI diseases and no alcohol or drug abuse as shown by a medical and physical exams were included in the study. Subjects should have no prescription drugs within 14 days, no alcohol consumption for at least 24 hours prior to drug administration, and no known allergy to ketorolac.

Exclusion criteria: included subjects with GI, renal, hepatic diseases, alcoholics, abnormal laboratory measurements, etc. No OTC medications nor alcohol, xanthine containing beverages were allowed during the study. Approved IRB as well as informed consent were obtained from each subject prior to entry into the study.

Subjects were housed in the facility from at least 12 hours prior to and at least 24 hours after the drug administration. Subjects were not permitted to smoke from one hour prior to and until 4 hours after the drug administration. Washout period was at least one (1) week between dose. Subjects were fasted for at least 10 hours prior to and 5 hours after the drug administration. Water was given ad lib except within 1 hour of drug administration.

Sampling schedule: 10 ml blood sample was collected at pre-dose, and at 0.17, 0.25, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 2, 4, 6, 8, 10, 12, 15, 24, and 36 hours. Plasma was separated and frozen at -20^{O}C until assay.

Assay Methodology:

Pharmacokinetic and statistical analyses: AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were calculated. ANOVA and 90% C.I. limits (two-one sided test) were used for all important pharmacokinetic parameters.

RESULTS

1 Analytical Methodology

2. Pharmacokinetics

According to the Sponsor, all 26 subjects completed the study. Minor adverse reactions such as emesis, diarrhea and light headache occurred in only three subjects (subj # 3, 10 and 24) and all were on reference formulation. No therapy was required. The Sponsor also indicated that no significant deviation from the study protocol, except some late blood draw. Mean plasma concentration-time profiles of all 26 subjects under test and reference treatments are shown below:

Mean Plasma concentration, ng/ml

Time (hr)	Test (%CV, N=26)	Ref (%CV, N=26)
0.	0.0	0.0
0.17	89.2 (143.6%)	118.1 (147.5%)
0.25	253.1 (108.2%)	396.1 (122.2%)
0.33	622.8 (83.4%)	878.4 (77.3%)
0.50	1402.6 (48.3%)	1489.1 (43.1%)
0.67	1460.2 (41.7%)	1441.3 (27.5%)
0.83	1383.3 (37.3%)	1368.6 (24.7%)
1.	1262.0 (37.1%)	1314.8 (24.4%)
1.25	1171.9 (28.3%)	1202.9 (24.8%)
1.5	1099.7 (26.2%)	1091.9 (22.1%)
2	969.1 (15.9%)	947.9 (22.5%)
4	565.0 (26.1%)	596.4 (31.5%)
6	343.2 (28.1%)	334.9 (30.4%)
8	226.3 (37.3%)	225.0 (30.4%)
10	177.6 (33.5%)	179.9 (48.7%)
12	126.7 (37.3%)	131.8 (47.3%)
15	73.9 (39.1%)	83.3 (45.5%)
24	24.8 (77.0%)	29.5 (60.1%)
36	0.0	0.0

Mean values of important pharmacokinetic parameters are shown below:

Parameter	Test (%CV)	Ref (%CV)
AUC_{0-t}	6423.6 (21.1%)	6655.0 (22.1%)
$AUC_{0-\infty}$	6722.4 (20.9%)	6943.5 (22.2%)
C_{max}	1733.0 (26.6%)	1713.0 (26.7%)

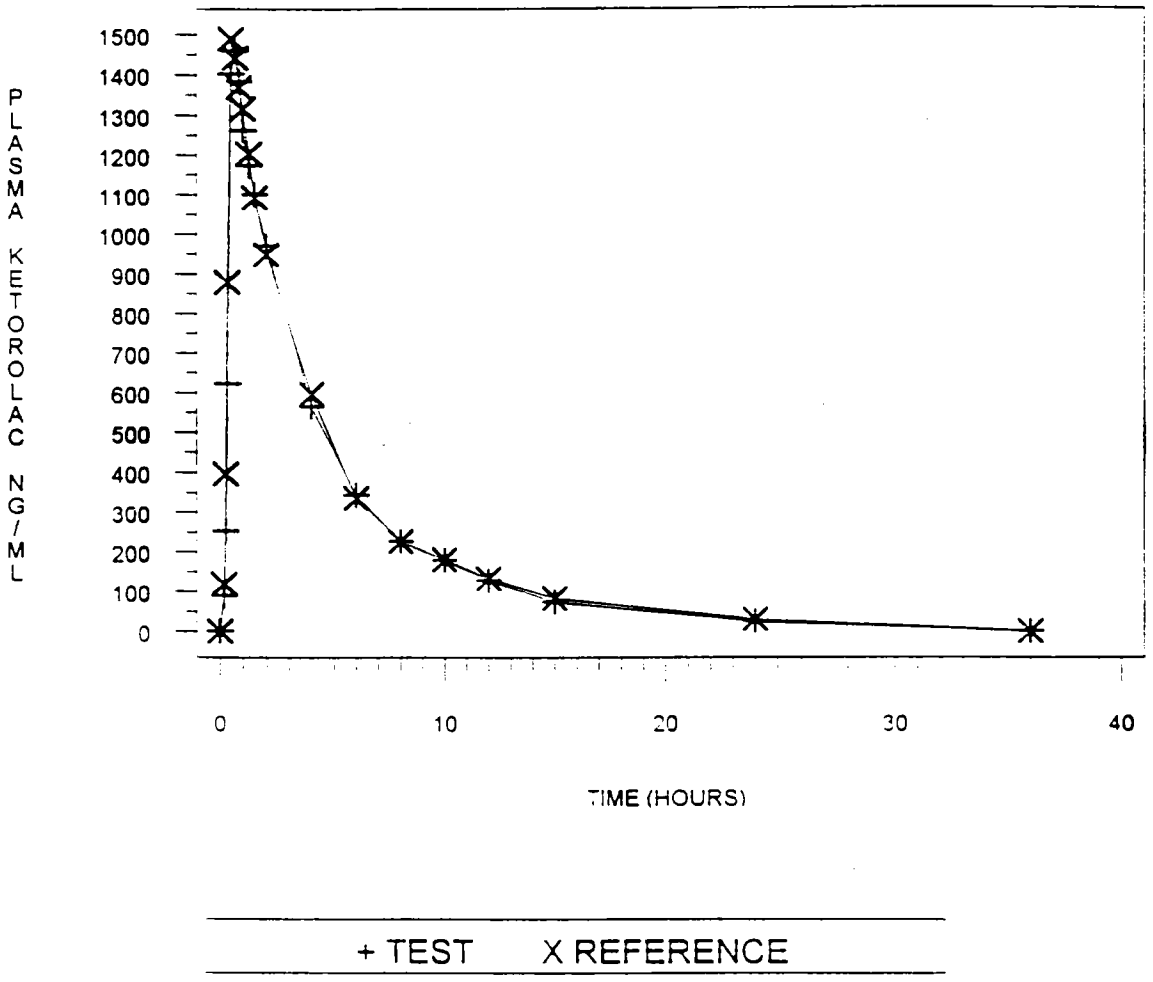
ANOVA was performed on all parameters and terms such as sequence, sub(sequence), period and treatment were included in the statistical model. 90% confident interval limits were estimated using two one-sided test procedure. Results indicated that, for log transformed and untransformed parameters, all parameters are within the current acceptable limits: AUCt (92.3% - 102%), AUCinf (92.9% - 102%) and Cmax (90.6% - 112%).

IV. Review of the non-fasting study: Protocol # B-01095.

Objective: To compare the bioavailability of a generic ketorolac tromethamine 10 mg tablets (Lemmon Company) with that of TORADOL^R 10 mg tablets by Syntex, in healthy male volunteers under fasting and fed conditions.
This will be a single dose, randomized, 3-way cross-over (test: fed and fasting, and reference: fed) in 18 subjects.

LINEAR PLOT OF

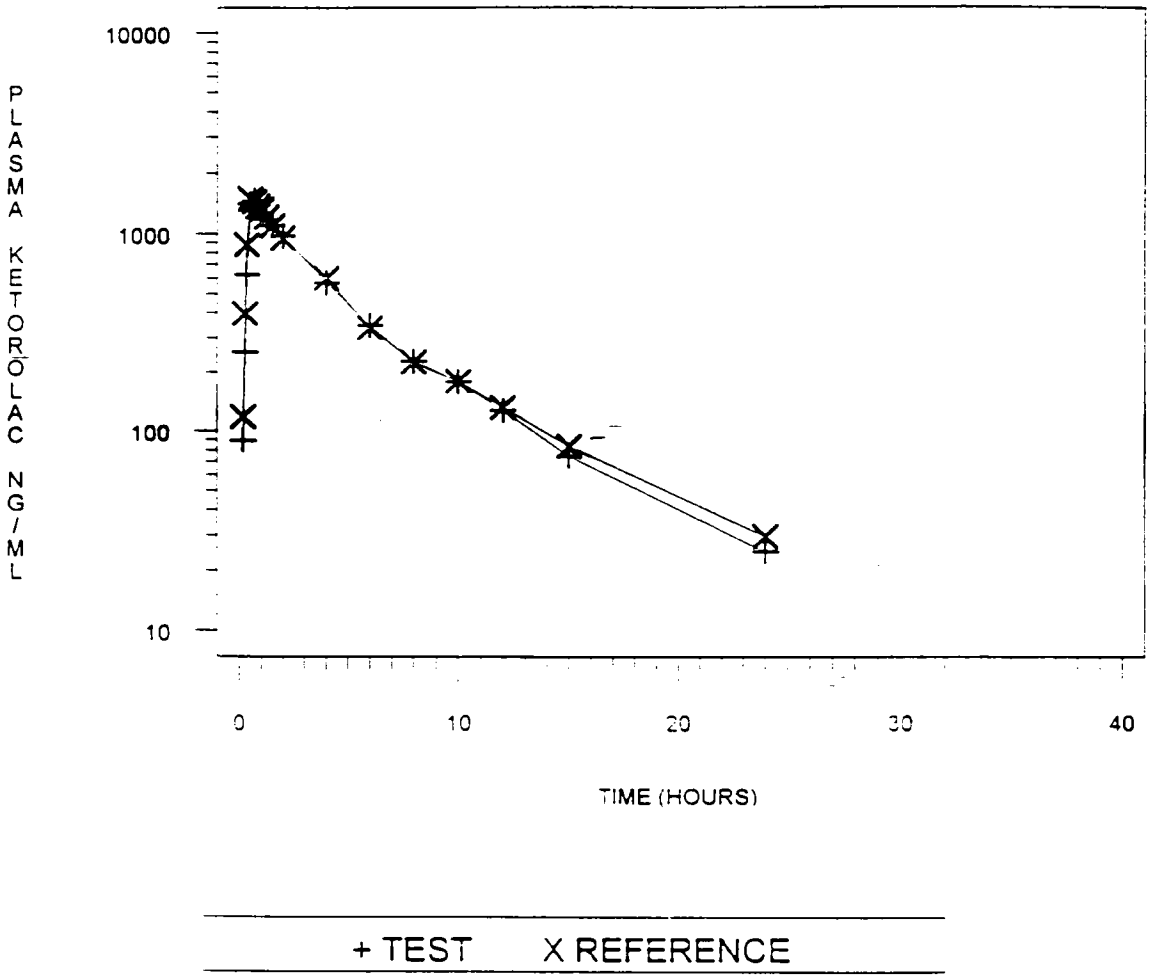
KETOROLAC MEAN DATA



+ TEST X REFERENCE

SEMI-LOG PLOT OF

KETOROLAC MEAN DATA



Principal Investigator:

Clinical Study Site:

Analytical Site:

Dose: Two (2) tablets with 240 ml of water. The lots of test and reference products used in the comparative studies are identical to the ones used in the fasting study as follows:

Test: LEMMON's ketorolac tromethamine tablets USP, 10 mg, lot # 0293-117, lot (batch) size: No expiry date, nor information on theoretical and actual yield were provided. Content uniformity: 99.2%.

Reference: SYNTEX's TORADOL^{R} (ketorolac tromethamine) 10 mg tablets, lot # 02541, expiry date: 2/96. Content uniformity: 98.7%.

Number of subjects: Eighteen males (18), with NO ALTERNATES The same subject selection criteria was used for the fasting and non-fasting studies.

Washout was one week between treatments.

Meal and food restriction:

Fed phase: Subjects will fast for at least 10 hours prior to serving the standard breakfast. Subjects will be instructed to eat the entire breakfast in 30 minutes and the drug will be given 35 minutes after the subjects begin the breakfast. Breakfast composition is as follows:

1 buttered English muffin
1 fried egg
1 slice of American cheese
1 slice of Canadian bacon
1 serving of hash brown potatoes
180 ml of orange juice
240 ml of whole milk.

Fasting phase: Subjects will fast for at least 10 hours prior to and 5 hours after drug administration.

Other procedures such as analytical, sampling schedule, are identical to the fasting study (Protocol # B-01085).

RESULTS

1 Analytical Methodology

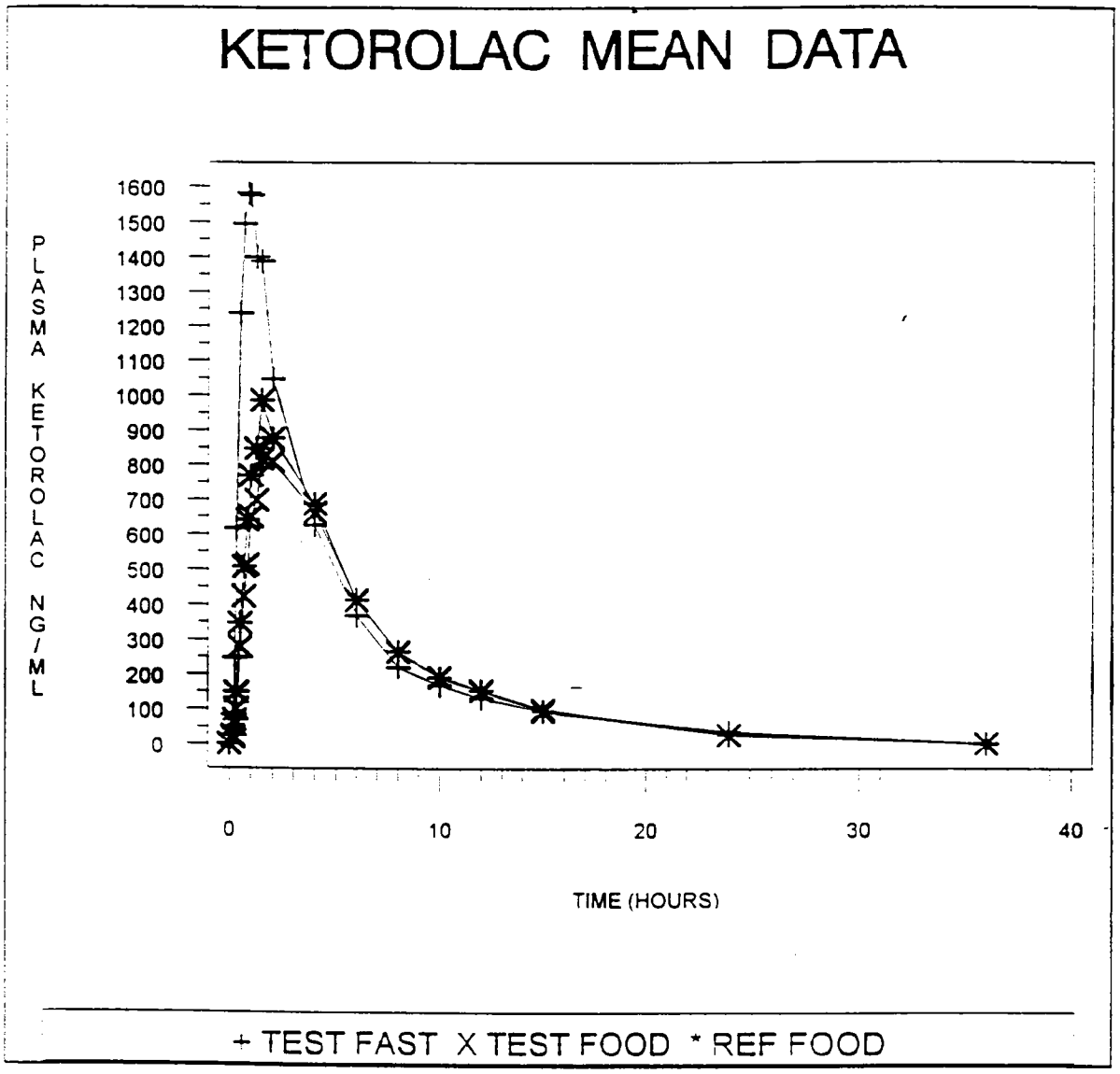
Since identical assay methodology was used for both fasting and non-fasting studies, no further assay validation data was submitted. No further information is needed on assay validation for this non-fasting study.

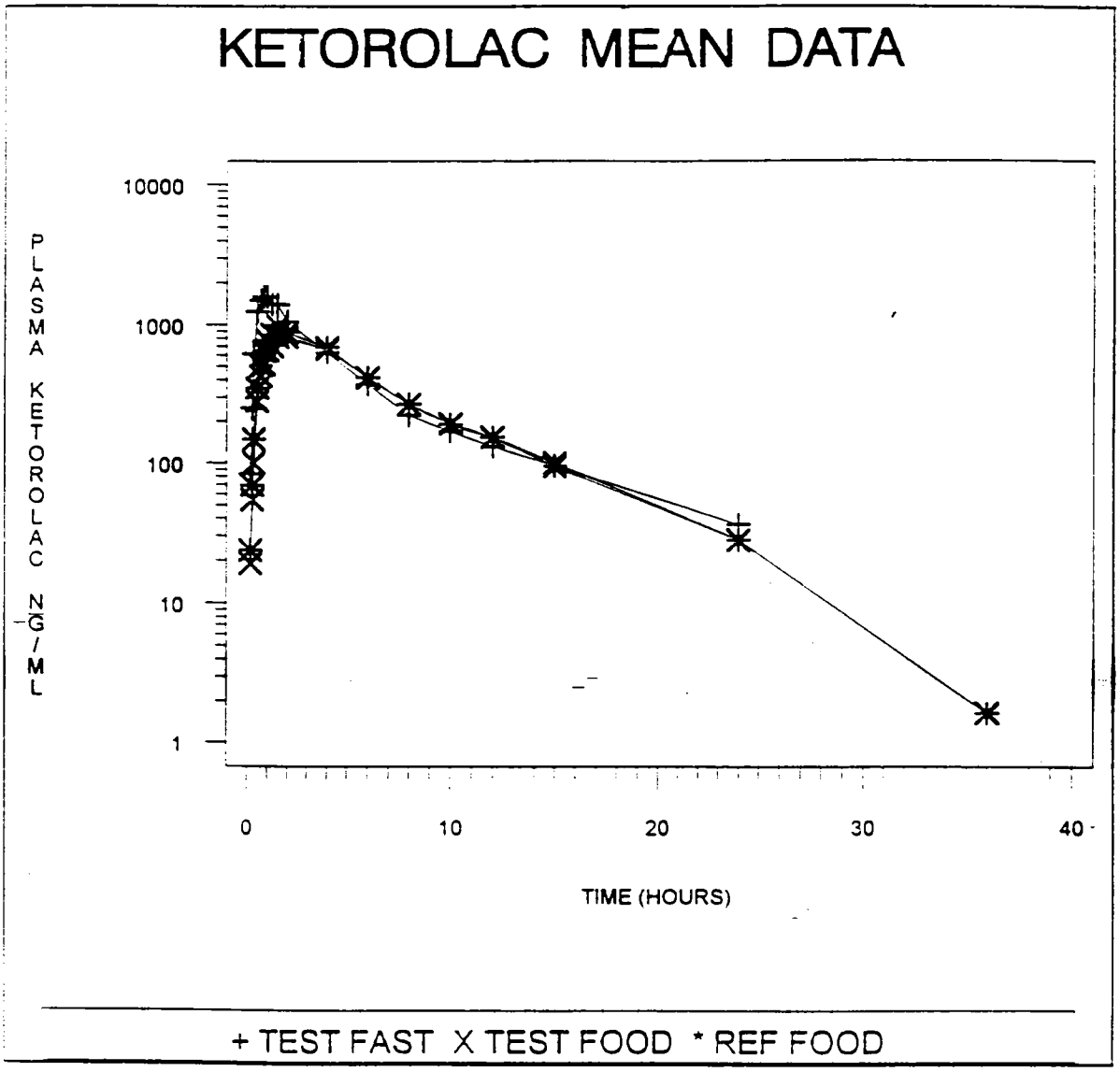
2. Pharmacokinetics

According to the Sponsor, of 18 subjects enrolled in the non-fasting study, 15 subjects completed the study. The firm reported the following drop-outs: subject #5 dropped prior to period 3 due to family situation, and 15 dropped prior to period 2 for personal reasons. The total number of subjects completing the study was 16. After the assay, the firm noticed that no valid data can be obtained from subject #9 due to problem with interferences in the chromatograms. Thus total number of subjects whose data were used for bioequivalence determination was 15. The Sponsor indicated that no adverse reactions nor protocol violations were observed in this non-fasting study, except some early or late blood draw times.

Mean plasma concentration-time profiles of all 15 subjects under fasting (test) and non-fasting (test and reference) conditions are shown below:

	Mean Plasma concentration, ng/ml		
Time (Hrs)	Test (%CV, N=15) (Fasting)	Test (%CV, N=15) (Fed)	Ref (%CV, N=15) (Fed)
0.	0.0	0.0	0.0
0.17	83.85 (76.51%)	19.01 (124.55%)	23.6 (82.24%)
0.25	248.25 (55.41%)	54.48 (85.45%)	68.93 (74.92%)
0.33	615.67 (79.90%)	100.59 (81.29%)	148.59 (97.93%)
0.50	1236.93 (51.83%)	279.93 (86.72%)	347.37 (81.54%)
0.67	1493.4 (27.91%)	423.86 (79.71%)	506.7 (71.61%)
0.83	1581.67 (31.04%)	512.84 (66.83%)	640.01 (72.96%)
1.	1575.87 (23.26%)	649.55 (62.29%)	768.60 (60.42%)
1.25	1399.47 (22.61%)	697.33 (50.98%)	845.80 (50.47%)
1.5	1388.0 (26.70%)	816.73 (55.45%)	985.13 (37.10%)
2	1046.6 (20.49%)	809.4 (33.32%)	876.07 (29.47%)
4	624.0 (25.38%)	661.73 (31.07%)	685.93 (29.40%)
6	369.0 (29.43%)	412.2 (36.18%)	413.53 (39.95%)
8	221.0 (24.49%)	265.09 (41.2%)	265.87 (39.65%)
10	169.66 (27.44%)	193.26 (43.54%)	191.31 (41.03%)
12	132.13 (27.62%)	153.62 (51.97%)	154.29 (45.00%)
15	95.43 (46.51%)	100.69 (53.30%)	94.56 (41.17%)
24	36.01 (61.39%)	27.93 (80.22%)	27.79 (72.28%)
36	0.0	1.65 (387.30%)	1.627 (387.30%)


KETOROLAC MEAN DATA
PLASMA KETOROLAC NG/ML
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30
40
TIME (HOURS)
+ TEST FAST X TEST FOOD * REF FOOD


KETOROLAC MEAN DATA
PLASMA KETOROLAC NG/ML
10000
1000
100
10
1
0
10
20
30
40
TIME (HOURS)
+ TEST FAST X TEST FOOD * REF FOOD

Means (N = 15) of important pharmacokinetic parameters are shown below:

Parameter	Test (%CV) (Fast)	Test (%CV) (Fed)	Ref (%CV) (Fed)
AUC_{0-t}	7136.83 (21.88%)	5992.38 (26.05%)	6266.08 (24.37%)
$AUC_{0-\infty}$	7528.05 (22.16%)	6302.95 (25.28%)	6569.65 (23.01%)
C_{max}	1936.60 (21.58%)	1055.20 (24.40%)	1198.47 (25.07%)

ANOVA was performed on all parameters and terms such as sequence, sub(sequence), period and treatment were included in the statistical model. From the ANOVA output, least squares means (log transformed data) of the test and reference formulations were obtained and they were used for the estimation of the ratios of test/reference for AUCt, AUCinf, and Cmax. For the log transformed data, this ratio can be estimated as $[100xe^{(LSMtest-LSMreference)}]$, with the least-squares mean (LSM) computed by using the LSMEANS statement in the SAS GLM procedure.

Results indicated that, for log transformed parameters, the ratios of the test and reference formulations under nonfasting conditions for ***AUCt (96.0%), AUCinf (96.2%) and Cmax (90.5%), all are within the current acceptable ratio limits of 80% to 125%.***

V. Composition of the test tablets

Core Tablet:

Ingredient	Amount per tablet
Ketorolac Tromethamine, USP	10 mg
Lactose Monohydrate, NF	
Microcrystalline Cellulose, NF	
Magnesium Stearate, NF	
Total	**200 mg**

Coating:

White

VI. In Vitro Dissolution Testing

The conditions and specifications used by the firm are identical to the ones by the USP as described below:

In Vitro Dissolution Testing

Drug: Ketorolac Tromethamine, Dose Strength: 10 mg, Tablet
ANDA No.: 74-754, Firm: Lemmon
Submission Date: September 21, 1995
File Name: 74754SD.995

I. Conditions for Dissolution Testing:

USP XXII, Paddle: RPM: 50, 600 ml, water, No. Units Tested: 12
Specifications: NLT › in 45 minutes
Reference Drug: TORADOL[R] 10 mg Tablets by SYNTEX.
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (min)	Test Product Lot # 293-117, Strength: 10 mg			Reference Product Lot # 2541, Strength: 10 mg.		
	Mean %	Range	%CV	Mean %	Range	%CV
15	89.6		13.5	93.5		8.2
30	97.3		7.4	98.1		4.9
45	99.0		5.5	100.3		3.6
60	99.7		4.4	101.3		3.0

VII. Deficiencies

1. For the fasting and fed studies, the estimation of Kel (hence AUCinf) is not reliable for the following subjects: For fasting study: subject 8 and 9 (test formulation) and subject 10 and 11 (reference formulation), and for the fed study: subject 4 and 6 (test formulation, fasting leg) and subject 2 and 6 (test formulation, fed leg) due to the irregularity of the terminal data points. Hence, it is suggested the firm should submit the following information for consideration:

a. Use appropriate pharmacokinetic model to fit the data of the above subjects, then estimate Kel and AUCinf. Re-do ANOVA and appropriate statistical testings.

b. Delete those subjects in the fasting and fed studies and redo statistical analysis of AUCinf for both studies.

Results of a) and b) should be submitted for comparative evaluation.

2. For the fed study, detail information on chromatographic interference on subject 9 should be provided. All chromatograms for this subject should be submitted for evaluation.

3. Data on photodecomposition of ketorolac should be provided. Comparative data on the extent of the stability of the samples under normal conditions and light-protected conditions should be provided. The extent of the photodecomposition of the samples by

4. Complete data with all calculations should be shown to substantiate the choice of using 1/Response as weighting factor vs. other weighting schemes, such as $1/(Response)^2$ or no weight in the regression of the standard curves.

5. Product Information: Since no expiry date, nor information on theoretical and actual yield were provided for the test formulation, the firm is requested to submit those information for review.

VIII. Recommendations

1. The bioequivalence studies conducted by Lemmon Company on its ketorolac tromethamine 10 mg tablets, Lot # 293-117, comparing it to Syntex's TORADOL^R Lot # 2541, 10 mg tablets, has been found incomplete by the Division of Bioequivalence due to Deficiencies 1 - 5 above.

2. The dissolution data submitted by the firm is acknowledged.

Nhan L. Tran, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED BY RPatnaik, Ph.D.
FT INITIALED BY RPatnaik, Ph.D. _____ 3/6/96

Concur: _____ Date: 3/6/96

/Keith Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA 74-754 (original), HFD-600 (OGD, Hare), HFD-630, HFD-344 (CTViswanathan), HFD-655 (Patnaik, Tran), Drug File, Division File.

SEP 27 1996

D IV

Ketorolac Tromethamine
10 mg tablet
Reviewer: Nhan L. Tran
ANDA 74-754
74754SD.596

Lemmon Pharmaceuticals
Sellersville, PA
Submission date:
May 14, 1996.

REVIEW OF A SUPPLEMENT

I. BACKGROUND

Ketorolac tromethamine is a chiral (R and S forms) non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, antipyretic and analgesic activities. Only the S form is reported to have analgesic activity. Ketorolac tromethamine is more than 99% protein bound, mostly bound to albumin.
When given orally, the bioavailability is at least 80% and the drug does not undergo first pass metabolism. Mean plasma Cmax is about 0.87 mcg/ml after single dose of 10 mg, with a Tmax of about 40 minutes. Plasma terminal half-life is about 5 to 6 hrs for the racemate. Ketorolac is mostly metabolized in the liver, and metabolic products are largely hydroxylated and conjugated forms of the parent drug.
Oral administration of ketorolac after a high fat meal results in lowering Cmax and prolonging Tmax by about 1 hour. The extent of absorption measured by AUC, and the half-life (T1/2) are not affected.
The drug is presently marketed by Syntex under the trade name TORADOL®, 10 mg tablets, and also is available in injectable dosage forms (15 mg, 30 mg and 60 mg for IM injection and 15 mg and 30 mg for IV Bolus injection).

The Sponsor submitted two biostudies (fasting and fed) on September 21, 1995. The studies were reviewed by the Agency on March 6, 1996 and it was found that the studies were deficient. In this supplement, the firm is responding to the deficiencies cited by the Agency in the review of March 1996.

II. SUMMARY OF THE STUDIES

Fasting study: Protocol # B-01085.

The objective of the study was to compare the bioavailability of a generic ketorolac tromethamine 10 mg tablets (Lemmon Company) with that of TORADOL® 10 mg tablets by Syntex, in healthy male volunteers under fasting conditions. The study was conducted at for Lemmon Company, with The analytical site was The dose was two (2) tablets and the number of subjects was 26 males with NO ALTERNATES.

The subjects were housed in the facility from at least 12 hours prior to and at least 24 hours after the drug administration. Subjects were not permitted to smoke from one hour prior to and until 4 hours after the drug administration. Washout period was at least one (1) week between dose. Subjects were fasted for at least 10 hours prior to and 5 hours after the drug administration. Water was given ad lib except within 1 hour of drug administration.
A ten (10) ml blood sample was collected at pre-dose, and at 0.17, 0.25, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 2, 4, 6, 8, 10, 12, 15, 24, and 36 hours. Plasma was separated and frozen at -20°C until assay.

Pharmacokinetic and statistical analyses: AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were calculated. ANOVA and 90% C.I. limits (two-one sided test) were used for all important pharmacokinetic parameters.

Non-fasting study: Protocol # B-01095.

The objective was to compare the bioavailability of a generic ketorolac tromethamine 10 mg tablets (Lemmon Company) with that of TORADOL® 10 mg tablets by Syntex, in healthy male volunteers under fasting and fed conditions.
This was a single dose, randomized, 3-way cross-over (test: fed and fasting, and reference: fed) in 18 subjects. The procedures, sites of clinical and analytical studies for this study, etc. were identical to the fasting study. The dose: Two (2) tablets, and the lots of test and reference products used in the comparative studies are identical to the ones used in the fasting study. Washout was one week between treatments.
Meal and food restriction:

Fed phase: Subjects were fasted for at least 10 hours prior to serving the standard breakfast. Subjects were instructed to eat the entire breakfast in 30 minutes and the drug was given 35 minutes after the subjects began the breakfast. Breakfast composition was as follows:

1 buttered English muffin
1 fried egg
1 slice of American cheese
1 slice of Canadian bacon
1 serving of hash brown potatoes
180 ml of orange juice
240 ml of whole milk.

Fasting phase: Subjects were fast for at least 10 hours prior to and 5 hours after drug administration.

Other procedures such as analytical, sampling schedule, were identical to the fasting study (Protocol # B-01085).

III. REVIEW OF THE RESPONSES

Deficiency 1: For the fasting and fed studies, the estimation of Kel (hence AUCinf) is not reliable for the following subjects: For fasting study: subject 8 and 9 (test formulation) and subject 10 and 11 (reference formulation), and for the fed study: subject 4 and 6 (test formulation, fasting leg) and subject 2 and 6 (test formulation, fed leg) due to the irregularity of the terminal data points. Hence, it is suggested the firm should submit the following information for consideration:
a. Use appropriate pharmacokinetic model to fit the data of the above subjects, then estimate Kel and AUCinf. Re-do ANOVA and appropriate statistical testings.
b. Delete those subjects in the fasting and fed studies and redo statistical analysis of AUCinf for both studies.
Results of a) and b) should be submitted for comparative evaluation.

Firm's response: The statistical analysis of AUCinf was re-run without the subjects with irregularities of the terminal data points. The 90% C.I. limits (log transformed) on AUCinf for the fasting study were 92.3% - 103%, while the ratio of the geometric means of the AUCinf for the fed study was 97.6%.
The firm's response is acceptable.

Deficiency 2: For the fed study, detail information on chromatographic interference on subject 9 should be provided. All chromatograms for this subject should be submitted for evaluation.

Therefore, we concur with the Sponsor that this subject should not be used for bioequivalent determination.
The response is acceptable.

Deficiency 3: Data on photodecomposition of ketorolac should be provided. Comparative data on the extent of the stability of the samples under normal conditions and light-protected conditions should be provided. The extent of the photodecomposition of the samples

Firm's response: The firm provided stability information as follows: For 24 hours at room temperature before extraction under normal conditions, the percent change

was -4.4, -4.9 and -5.4 for high (2500 ng/ml), medium (350 ng/ml) and low (50 ng/ml) concentrations respectively. Under light protected conditions, for 24 hours at room temperature before extraction, the percent change was comparable to the one under normal conditions, i.e., -3.5, -4.3, and -5 for high, medium and low concentrations. The stability of ketorolac in was demonstrated after 5 and 10 minutes exposure.
The response is acceptable.

Deficiency 4: Complete data with all calculations should be shown to substantiate the choice of using 1/Response as weighting factor vs. other weighting schemes, such as $1/(Response)^2$ or no weight in the regression of the standard curves.

Firm's response: Based on the data submitted using different weighting factors such as 1/C, $1/C^2$ and unweighted linear regression, the contract laboratory uses 1/C as the weighting factor for the regression of the standard curves.
The response is acceptable.

Deficiency 5: Product Information: Since no expiry date, nor information on theoretical and actual yield were provided for the test formulation, the firm is requested to submit those information for review.

Firm's response: Theoretical yield was ablets and actual yield was tablets. Ratio of actual/theoretical was . The response is acceptable.

IV. .RECOMMENDATIONS

1. The fasted and nonfasted bioequivalence studies conducted by Lemmon Company on its ketorolac tromethamine 10 mg tablet, Lot # 293-117, comparing it to Syntex's TORADOL[R] 10 mg tablet, Lot # 2541, has been found acceptable to the Division of Bioequivalence. The studies demonstrate that Lemmon's ketorolac tromethamine 10 mg tablets are bioequivalent to the reference product,.Syntex's TORADOL[R] 10 mg tablets.

2. The dissolution testing conducted by Lemmon Company on its ketorolac tromethamine 10 mg tablet, Lot # 293-117, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 600 ml of water at 37°C using USP XXIII Apparatus II (**Paddle**) at 50 rpm. The test product should meet the USP specifications:

> Not less than of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

From the bioequivalence point of view, the firm has met the ***in-vivo*** bioequivalence and ***in-vitro*** dissolution requirements and the application for Lemmon's ketorolac tromethamine 10 mg tablets, ANDA 74-754 is acceptable.